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Atrial fibrillation: all the elderly go hospitalized? A minireview

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Atrial fibrillation (AF) is a very common in clinical practice. The prevalence of AF is high after the age of 65 years. Patients with AF have a worse quality of life than healthy controls. However, concomitant higher hemorrhagic risks, severe cognitive and functional impairment may at least partly explain under-prescription of oral anticoagulants in the elderly.

EPIDEMIOLOGY

Patients with Atrial fibrillation (AF) are at greater risk for thromboembolic events, hospitalization, heart failure and death [1-3]. Clinical risk factors for AF are reported in Table I. The prevalence of AF is high after the age of 65 years and it is 1.5 times more frequent in men than women [4-5]. For example, the prevalence rate in males 75-79 aged is doubled compared to males aged 65-69 years and more than 5 times greater than males 55-59 years old [6]. However, in the European Union by 2030, about 120.000-215.000 newly diagnosed patients per year are estimated [7].

TYPES

Traditionally there are five types of Atrial fibrillation [7]:

- first diagnosed atrial fibrillation. Atrial fibrillation that has not yet been diagnosed, not taking into account the duration of the arrhythmia, the presence and severity of symptoms;
- paroxysmal atrial fibrillation. Atrial fibrillation ends spontaneously in the first 48 hours in most cases. Some AF can last up to 7 days. An episode of AF with a cardioversion within seven days should still be considered paroxysmal;

Table I. Clinical risk factors for atrial fibrillation.

Advanced age
Diabetes
Hypertension
Congestive heart failure
Rheumatic and non-rheumatic valvular disease
Myocardial infarction

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- persistent atrial fibrillation. Atrial fibrillation that lasts more than 7 days. Also episodes where there is a cardioversion with both drugs and dc-shock after 7 days or more;
- long-standing persistent atrial fibrillation. Continuous AF that lasts for ≥ 1 year when you decide to use rhythm control;
- permanent atrial fibrillation. Atrial fibrillation that is accepted by the patient (and physician).

SIGNS AND SYMPTOMS

Patients with AF have a worse quality of life than healthy controls. They develop a range of symptoms ranging from lethargy, palpitations, dyspnea, chest pain, difficulty sleeping and psychosocial distress. In Emergency department it's not uncommon to find patients with signs of congestive heart failure (as pulmonary edema, peripheral edema, ascites) or with signs of embolism (ischemic attack transient, or stroke) [7].

MANAGEMENT

In the Emergency Department in the evaluation of AF play a fundamental role, a history and physical examination, specific laboratory and cardiological tests.

History and physical examination

Not all patients with AF are symptomatic, so the history and physical examination must focus on a few key points [8]:

- description of symptoms, focusing on the severity and qualitative characteristics of the symptoms;
- possible precipitating causes;
- the presence of associated pathologies such as, cardiovascular or cerebrovascular diseases, diabetes, hypertension, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, alcohol and hyperthyroidism, which can be potentially reversible, causes;
- cardiopulmonary and neurological examination is essential because they can highlight the presence of complications such as congestive heart failure or stroke.

EKG

The electrocardiogram, (EKG), (class IB) is necessary to make the diagnosis. AF has the following electrocardiographic characteristics [7]:

- the RR intervals follow no repetitive pattern;
- there are no distinct P waves.

Echocardiography

A transthoracic echocardiography (classed IC) is another crucial exam to do because it is important to know:

- the size of the atria. In fact, large atria could orient to a long-term AF and lean towards a more conservative therapeutic strategy;
- structural anomalies. In particular, it can guide *vs* the use of rhythm control drugs (as amiodarone) rather than others (as flecainide and propafenone).

Certainly transthoracic echocardiography has a very low sensitivity to recognize the presence of atrial thrombi. In this case it is necessary to carry out a trans esophageal echocardiography [7-8].

Baseline laboratory testing

Baseline tests test include [7]:

- thyroid evaluation. In particular, hyperthyroidism is present in less than 5% of patients with AF. Generally we should have in all the patients with AF a TSH and free T4 (9-10);
- complete blood count;
- serum creatinine;
- analysis for proteinuria;
- test for diabetes mellitus;
- test to study possible risk factors and concomitant diseases.

CLUSTER DISEASE

Hypertension and coronary heart disease are the most common diseases found in patients with AF in developed countries. The rheumatic disease, still very present in developing countries, is very much associated with the incidence of AF. Cluster diseases associated to AF are reported in Table II.

Hypertensive disease

Hypertension is the most common disorder present in patients with AF. Also due to the high frequency of hypertension in the general population, the history of hypertension increased the risk of developing AF about 1.42 fold [11].

Table II. Cluster Diseases associated to atrial fibrillation.

Hypertensive disease
Coronary disease
Valvular heart disease
Heart failure (HF)
Venous thromboembolic disease
Chronic obstructive pulmonary disease
Obstructive sleep apnea syndrome
Obesity
Diabetes
Chronic kidney disease

Coronary disease

Atrial fibrillation occurs in 6-10% of patients with acute myocardial infarction. These patients also have a poorer prognosis, and have a mortality increase at 30 days and 1 year [12].

Valvular heart disease

Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. In a review of 89 patients with mitral valve prolapse and 360 with flail leaflets, the rate of development of AF was about 5% per year [13]. Atrial fibrillation is an infrequent (about 1%) in patients with aortic valvular diseases. Left atria and age are the most important parameters to determine the occurrence of AF in patients with rheumatic heart disease [13,14].

Heart failure (HF)

Atrial fibrillation and heart failure (HF) often occur together and each of the two can predispose to the other. Atrial fibrillation is found in more than one half of individuals with HF. These data are particularly interesting, because knowing that one third of people with AF can develop Heart Failure; it's possible to start a prevention of HF and prevention of stroke [15].

Venous thromboembolic disease

The risk of Atrial fibrillation is increased in patients with Deep Vein Thromboembolism or Pulmonary thromboembolism. The mechanism is not known, but is probably due to the increase in pulmonary vascular resistance and to the right post cardiac loading that cause a right atrial strain. Pulmonary thromboembolism is more frequently associated with AF than Deep Vein Thromboembolism [16].

Chronic obstructive pulmonary disease

In patients with chronic obstructive pulmonary disease it has been shown that the reduction of FEV_1 correlates with an increase in the incidence of AF [17].

Obstructive sleep apnea syndrome

There is a possible causal relationship between obstructive sleep apnea syndrome (OSAS) and AF. A history of hypoxemia and hypercapnia may lead to an increase in circulating catecholamine that may predispose to AF. In addition, the presence of numerous increased inflammation factors in patients with OSAS may predispose to AF [18].

Obesity

Obese individuals (as body mass index [BMI] > 30 kg/m^2) are significantly more likely to develop AF than those with a normal BMI (< 25 kg/m^2). In the Framingham Heart Study, every unit increase in BMI was associated with about 5% an increase in risk [19].

Diabetes

In the Framingham Heart Study (over 4700 individuals without valvular heart disease), the presence of diabetes was associated with a significantly increased risk for the development of AF [20].

Chronic kidney disease

Chronic kidney disease (CKD) increases the risk of the development of AF. In patients with CKD there are several reasons to develop AF. They tend to have higher pression values and an overload of fluids that can lead to ventricular hypertrophy, atrial stretch, and fibrosis. In addition CKD patients have an up-regulated renin-angiotensin-aldosteron (RAA) system that can cause remodeling of the heart chambers and predispose to AF [21].

TREATMENT

A key point for the management of AF for the healthcare providers is to know if is new or old onset AF.

Rate *vs* rhythm control

Rate control is indicated in hemodynamically stable patients with AF more than 48 hours, in which immediate cardioversion cannot be performed. The rationale for rate control is to avoid hemodynamic instability, improve symptoms and avoid tachycardia-mediated cardiomyopathy.
There are two frequency targets [22]:

- < 80 beats/min at rest and < 110 beats/min under stress;
- < 110 beats/min.

It is not clear what the best strategy is, but above all in the initial phases, more delicate management can be accepted [7]. In the presence of structural heart disease, it is recommended amiodarone (loading dose: 5-7 mg/kg over 1-2 hours; and follow-up dose 50 mg/hour to maximum of 1.0 g over 24 hours). Amiodarone has an efficacy comparable to the drugs of the class Ic (as flecainide, 1.5-2 mg/kg over 10 min iv or propafenone, 1.5-2 mg/kg over 10 min) in the return to sinus rhythm in the first 24 hours. The drugs of the class Ic show a more rapid onset of action, with some effects already after 1-2 hours after administration [24,25]. It is crucial avoid these drugs (class Ic) in the presence of structural heart diseases.
Rhythm control can be obtained with two methods:

- pharmacological or electrical cardioversion.

Pharmacological cardioversion

The drugs used in the rhythm control (class IB) are reported in Table III. A disadvantage of pharmacological cardioversion is that the patient must be observed for at least 50% of the half-life, so as to check the pro-arrhythmic effects of these drugs [7,23].

Table III. The drugs used in the rhythm control (class IB).

Beta blockers
• Metoprolol (2.5-10 mg intravenous bolus, repeated as required)
• Esmololo (0.5 mg/kg intravenous bolus over 1 min; then 0.05-0.25 mg/kg/min)
Calcium channel blockers
• Verapamil (2.5-10 mg intravenous bolus)
or
• Diltiazem (15-25 mg intravenous bolus) (both repeated as required)
Digoxin
0.5 mg intravenous bolus and after 0.75-1.5 mg over 24 hours in divided doses

The management of the AF with rhythm control offers no advantages compared to the rate control or rather can be aggravated by numerous side effects [26].

Electrical cardioversion

In hemodynamically unstable patients, an emergency electrical cardioversion is indicated [7]. It has a success rate ranging from 67-94%, remains a very safe technique and the most effective in ending AF. It is necessary to obtain sedation analgesia with drugs, such as Fentanyl, Midazolam, or Propofol. The risks of this procedure are related to sedation, as skin burns and pro-arrhythmias, which are very rare since the shock is synchronized with the QRS [23].

PREVENTION OF EMBOLIZATION

Various trials and meta-analyzes have shown how the use of an antithrombotic therapy reduces the onset of stroke [26-28]. For the choice to make or not an anticoagulant therapy it is necessary to be guided by the CHA_2DS_2-VASc score. In particular, oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHADS-VASc score of 2 or more, and of 3 or more for all female with AF (class IA).

The drugs of choice are:

- warfarin;
- direct thrombin inhibitors as dabigatran;
- inhibitors of factor Xa (as rivaroxaban, apixaban, edoxaban);

The oral anticoagulant (NOACs) seem to have better clinical benefits and a better safety profile with regard to bleeding, than warfarin, in particularly in the elderly and the frailty elderly [7,28-34]. Although the use of NOACs is associated with a reduction in bleeding, about 2.1-3.6% of major bleeding is found [35]. To this regard, two specific antidotes were approved by the FDA, as idarucizumab for dabigatran, and alpha-andexanet for apixaban e rivaroxaban [36]. In addition, non-specific prohaemostatic agents have also been used, as prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (APCC). For the management of life-threatening bleeding or bleeding in critical organs, or major bleeding that do not respond to supportive therapies, it is recommended to use antidotes or non-specific prohemostatic agents, while in other bleeding is not recommended. In fact in other bleeding are recommended:

- withdrawal of NOACs and other drugs that interfere with coagulation (as antiplatelet);
- direct compression of the bleeding site;
- volume resuscitation and transfusion.

For patients with mucosal bleeding (epistaxis and uterine bleeding) anti-fibrinolytic therapy is recommended. In cases of suspected overdose, oral activated charcoal may be useful to reduce absorption if it occurred in the last hours [36].

NOACS IN ELDERLY

Female patients with AF are older, with more frequent cognitive and functional impairment, and higher rate of comorbidity than males [37,38]. The risk of stroke is known to increase with increasing age [39]. Aspirin is still used in patients over 75 years of age, because considered more convenient. Numerous trials (as BAFTA trial and AVERROES trial) demonstrated how warfarin and NOACs are more effective and safety than aspirin [40,41]. In patients over 90 years of age, warfarin and NOACs are more effective in reducing stroke, and NOACs are more effective in reducing intracranial hemorrhage (ICH) than warfarin [42]. The best drugs for the prevention of embolization in elderly patients remain the NOACs, even if only 16.1% of very elderly population receives the NOACs [42].

PREVENTION OF EMBOLIZATION IN CKD

Numerous studies have been carried out on patients with CKD and AF, especially regarding the issue of prevention of embolization. CKD alone is a risk factor for stroke and prothrombotic states. In moderate CKD, is recommended both warfarin and reduced dose of NOACs (as reported in Table IV). In the case of end stage renal disease and hemodialysis patients there are no very decisive studies. The NOACs have a greater renal metabolism compared to warfarin. In particular, dabigatran almost completely metabolized via the kidney (80%) and apixaban instead only a small part (25%). The FDA authorized the use of apixaban and rivaroxaban in these patients. The AHA/ ACC/ HRS recommended warfarin in this type of patients even if numerous studies are still necessary [43]. In patients with chronic kidney disease, the use of low molecular weight heparin (LMWH), as enoxaparin, remains quite safe, even

Table IV. The NOACs in patients with CKD moderate.

Dabigatran (110 mg bis in die)
Apixaban (2.5 mg bis in die)
Rivarxaban (15 mg once daily)
Edoxaban (30 mg once daily)

in those patients with glomerular filtration rate below 30 ml/min/1.73 m^2, with a dosage of 1 mg/kg once daily [44].

INDICATIONS FOR HOSPITALIZATION

Most of the new-onset AF agents are not hospitalized. Possible indications for hospitalization of patients with new-onset AF are reported [45]:

- patients considering ablation. Especially if very symptomatic associated with elevated ventricular response or haemodynamically unstable;
- patients with severe bradycardia post cardioversion;
- treatment of other concomitant pathologies of AF (as exacerbation of chronic obstructive pulmonary disease, thyrotoxicosis, infections, pulmonary embolism, coronary syndrome);
- treatment of elderly patients. In fact, in these patients embolic events are more easily found and very often have numerous comorbidities [46];
- start of a chronic rhythm control therapy;
- management of heart failure and hypertension after control of the rhythm or the control rate.

CONCLUSIONS

Prevention of thromboembolic risk in elderly with AF is an imperative clinical need. However, concomitant higher hemorrhagic risk and other characteristics that were more frequent in elderly patients (as severe cognitive, CKD, comorbidity and functional impairment) may at least partly explain the under-prescription of oral anticoagulants in these patients.

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