Atrial fibrillation and stroke risk prevention in the elderly

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in medical practice (1). Its prevalence increases with age; starting at the age of 50, this doubles every decade of life, corresponding to a 5% prevalence in the population older than 60, and a 13% prevalence in the population older than 80. This means that 70% of cases affect people who are between 65 and 85 years old (2). This is due to the increase in the prevalence of predisposing factors that can trigger the onset of arrhythmia that occur with age, for example, changes in tissue and heart structure, systemic diseases, and the use of medications that induce arrhythmia, as well as other factors.

When an episode of AF lasts longer than 48 hours, there is an increased risk of intra-atrial thrombi formation. Atrial thrombi can migrate through blood vessels and cause a thromboembolic phenomenon (TEP) (3), which constitutes the most common and serious type of complication associated with AF. These thrombotic events can either affect the central nervous system (e.g., causing an ischemic stroke) or they can be peripheral. Therefore, treatment for the primary and secondary prevention of such complications based on risk stratification (2, 4-5) is important and should be prescribed, except in the presence of contraindications, such as organic, psychosocial, and geographical factors (1, 6-15).

The drugs used for primary and secondary prevention are oral anticoagulants (OAC) and antiplatelet agents, the latter being less effective than the former. However, in daily practice, OACs are often underused, especially among the elderly, due to the fear of possible hemorrhagic complications rather than the presence of true contraindications (3).

Risk factors and thromboembolic phenomena

In patients with AF, the risk factors for thromboembolic phenomena are considered either cardiac or independent. Among the former are valvulopathy (e.g., prosthetic valves, mitral stenosis), congestive heart failure (CHF), coronary artery disease, a left atrial diameter greater than 5 mm, and hypertrophic cardiomyopathy. The independent risk factors include a previous history of cerebral ischemia, systemic arterial hypertension (SAH), diabetes mellitus (DM), peripheral arterial disease, thyrotoxicosis, female gender, and advanced age (2).

These risk factors have different degrees of influence in terms of an individual's predisposition to TEPs, that is, the presence of one risk factor may imply a higher risk than another. These risk factors can be stratified as follows: 1) low risk: female gender, age between 65 and 75 years, coronary artery disease (CAD), and thyrotoxicosis; 2) moderate risk: 75 years of age or older, SAH, CHF, a ventricular ejection fraction (VEF) ≤35%, and DM; and 3) high risk: a previous ischemic stroke or transient ischemic attack (TIA), mitral stenosis, and the presence of a prosthetic heart valve (2).

Age is an independent risk factor that is associated with a moderate increase in the risk of the occurrence of TEPs. In other words, even in the absence of other risk factors, an elderly person with AF and no other risk factors for TEP may suffer such a complication. TEPs can cause serious sequelae, because, generally, 2/3 of them affect the central nervous system and evolve, in 70% of cases, into serious and irreversible complications or death.

Beyond the fact that age is an independent risk factor and that these patients may have serious sequelae from TEPs, another important point is that the incidence of ischemic stroke, like that of AF, increases progressively with age. Until the age of 60, the risk of stroke per year is 1.5%. It increases to 5% per year for individuals between 60 and 75 years old, is 8.3% per year for people who are 75 years old, and can reach as high as 23% per year for octogenarians (2). Moreover, the risk of cerebral hemorrhage due to the use of OACs is greater in patients who are over 80 years of age; thus, the age group with the greatest need for prevention through anticoagulation is the same group that is most likely to suffer from its side effects. Therefore, a careful risk-benefit analysis must be performed is important in order to avoid both unnecessary anticoagulation and undue contraindications.

Risk stratification and indications for anticoagulation

Risk stratification strategies to select the patients who might benefit the most from anticoagulation have been evaluated in some studies that have used a risk score for ischemic stroke. This risk score assigns points to each risk factor and the resultant sum approximates the risk of ischemic stroke.

The Framingham score (4) considers female gender, the progression of age, SAH, DM, ischemic stroke, and previous episodes of cerebral ischemia as risk factors (RF) for ischemic stroke. A Framingham score ≤7 is considered low-risk, a score between 8 and 13 is considered medium risk,

and a score between 14 and 31 is considered high risk. In practice, this score has not been used to determine who should receive anticoagulant therapy.

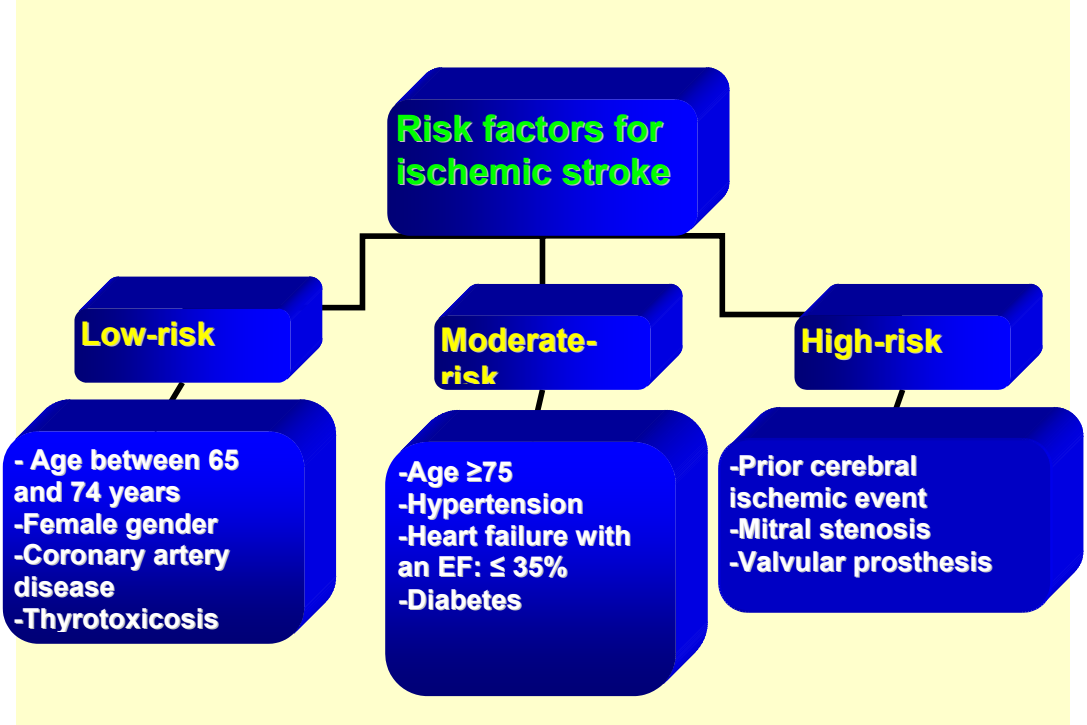
The CHADS2 score (**C**ardiac failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke) (5), assigns the presence of congestive heart failure with an ejection fraction less than 35%, hypertension, diabetes, and age >75 one point each of and a personal history of ischemic stroke and/or transient ischemic attack two points. A score of zero points means that a patient is low-risk, a score between one and two means that a patient is moderate-risk, and a score between three and six means that a patient is high-risk. Anticoagulation is indicated for those who have a CHADS2 score of two or higher.

CHADS2 Score
Cardiac failure – 1
Hypertension – 1
Age > 75 – 1
Diabetes mellitus – 1
Stroke or transient ischemic attack – 2

The international guidelines for AF (2) cite the CHADS2 score, but add valvulopathy and thyrotoxicosis to the risk stratification and suggest the use of anticoagulants in patients who have one high-risk risk factor or more than one moderate-risk risk factor. For those who have a single moderate risk factor, the guidelines suggest the use of either aspirin or oral anticoagulants. For patients with AF who have no risk factors, the guidelines recommend using aspirin (acetylsalicylic acid—ASA) for TEP prevention.

According to the current guidelines, there is unanimous agreement that patients older than 75 years of age (even those without any other RFs) as well as patients between 65 and 75 years of age with at least one risk factor, benefit from prevention.

Considering that the diseases that are considered risk factors (DM, SAH, CAD, etc.) most commonly affect the elderly (those >65 years), the majority of patients with AF would benefit from primary prevention.



Medications for TEP Prevention

The drugs classically tested and recommended for TEP prophylaxis include OACs (warfarin) and antiplatelet agents (ASA) (1-2, 6-15).

Randomized studies performed between 1989 and 1992 (6-7, 11, 13-15) compared the use of warfarin, aspirin, and/or a placebo, with regard to efficacy of TEP prevention in patients with atrial fibrillation (1-7). The mean follow-up period in these studies varied from 15.2 to 26.4 months. The results demonstrated that OACs are more effective than ASA in the primary and secondary prevention of TEPs in patients with AF (16).

The AFASAK study (7) compared the use of warfarin, aspirin, and a placebo in terms of TEP prevention in 1007 patients. In this study, patients' international normalization ratio (INR), which measures the intensity of blood anticoagulation, was controlled between 2.8 and 4.2 and the dose of aspirin was 75 mg. Five ischemic stroke events occurred in the warfarin group, 20 occurred in the aspirin group, and 21 occurred in the placebo group. In the warfarin group, 21 patients were withdrawn because of non-fatal bleeding complications compared with 2 on aspirin and none on placebo. The efficacy of prevention was 59% with anticoagulants and 16% with aspirin (CI 95%).

The BAATAF study (8) randomized 212 patients to warfarin (with an INR between 1.2 and 1.5) and 208 patients to aspirin. Two ischemic strokes occurred in the first group and thirteen in the second. The effectiveness of prevention with anticoagulant use was 86% (CI 95%).

The SPAF I study (9-12) compared the use of warfarin (with an INR level between 2 and 4.5), aspirin (325 mg), and placebo in TEP prevention in patients with AF. There was a risk reduction of 69% in the warfarin group. Six patients in the warfarin group had an ischemic stroke, but they were not using the medication correctly during the time of the event. In contrast to the other studies, which showed that aspirin did little to prevent TEPs, the effectiveness of prevention of aspirin was 42% in this study.

However, there was controversy regarding the selection of patients for this study, because isolated AF was included and some TEP risk factors were used as exclusion criteria. Therefore, the patients in this study had a lower risk of ischemic complications than the cohorts included in other studies. SPAF II (10, 12) followed SPAF I. In SPAF II, there was no placebo group and patients were split into two groups based on age (<75 and ≥75).

The results of SPAF II showed that warfarin was more effective than aspirin in the prevention of TEPs in both groups and that the older patients on warfarin suffered more cerebral hemorrhages than those who took aspirin. Nevertheless, the goal of the intensity of anticoagulation went INR 2.0 – 4.5 (12). SPAF III (11-12) classified patients as high-risk or low-risk with regard to the occurrence of TEPs. Those who had systolic BPs greater than 160 mmHg, left ventricular dysfunction, CHF, previous TEPs, as well as those who were female and those older than 75 years of age were considered high-risk and randomized into two groups: one that received OACs with a goal INR between 2 and 3 and another that received aspirin (325 mg) mixed with an OAC with a goal INR between 1.2 and 1.5, measured at 3-month intervals. The study ended prematurely because the group with the lower goal INR exhibited more ischemic events, whereas the group with an INR between 2 and 3 exhibited a significant decrease in the risk of TEPs.

Researchers from the CAFA study (13) began a double-blind, controlled study to evaluate warfarin compared with a placebo for TEP prevention in patients with AF. However, when the initial results of the AFASAK and SPAF studies illustrated the superiority of the anticoagulant over aspirin, the study ended early so that the enrolled patients could receive warfarin therapy.

The researchers from the SPINAF study (14) compared warfarin with a placebo and concluded that the anticoagulation exhibited a 79% risk reduction for ischemic stroke.

After the aforementioned randomized studies regarding primary prevention for TEPs had been completed, the EAFT study (15) investigated the effectiveness of warfarin and aspirin for secondary prevention compared with a placebo. The effectiveness of warfarin was 66% and that of aspirin was 18%. The rate of ischemic stroke in the placebo group was 12% per year, in which was higher than the rates observed in the studies on primary prevention.

In 1999, a meta-analysis of five of the initial studies (6) concluded that anticoagulation is highly effective in the prevention of ischemic stroke with a risk reduction of 65% (95% CI: 52% - 74%), while aspirin reduced the risk of ischemic stroke by 23% (95% CI: 0% - 40%) when compared to placebo. When compared with each other, warfarin had a risk reduction of 46% as compared to aspirin (95% CI: 27% - 60%).

In 2002, the authors of the AFFIRM study (17) published their results evaluating what is the best better strategy in patients with AF: rate control or rhythm control.

Throughout the follow-up period, OACs were appropriately prescribed for TEP prophylaxis based on the existence of validated studies in the literature demonstrating that OAC use decreased the risk of TEPs in patients with AF. The authors concluded that, independent of the chosen strategy (rate vs. rhythm control), adequate anticoagulation was the most important factor in the prevention of thromboembolic events in the patients evaluated.

The ACTIVE study (a multicenter, double-blind, randomized trial) compared warfarin and clopidogrel in patients with AF and risk factors for stroke in its “W” trial. Clopidogrel was observed to be inferior in relation to warfarin for TEP prevention, leading to an early discontinuation of this trial (16).

A 2007 meta-analysis (18) evaluated 13 studies and concluded that warfarin reduces the risk of ischemic stroke by 64% and aspirin reduces the risk of ischemic stroke by 22%; thereby concluding that warfarin was more effective than aspirin with a relative risk reduction of 39%. The increase in the risk of intracranial hemorrhages was 0.3% per year in the warfarin group.

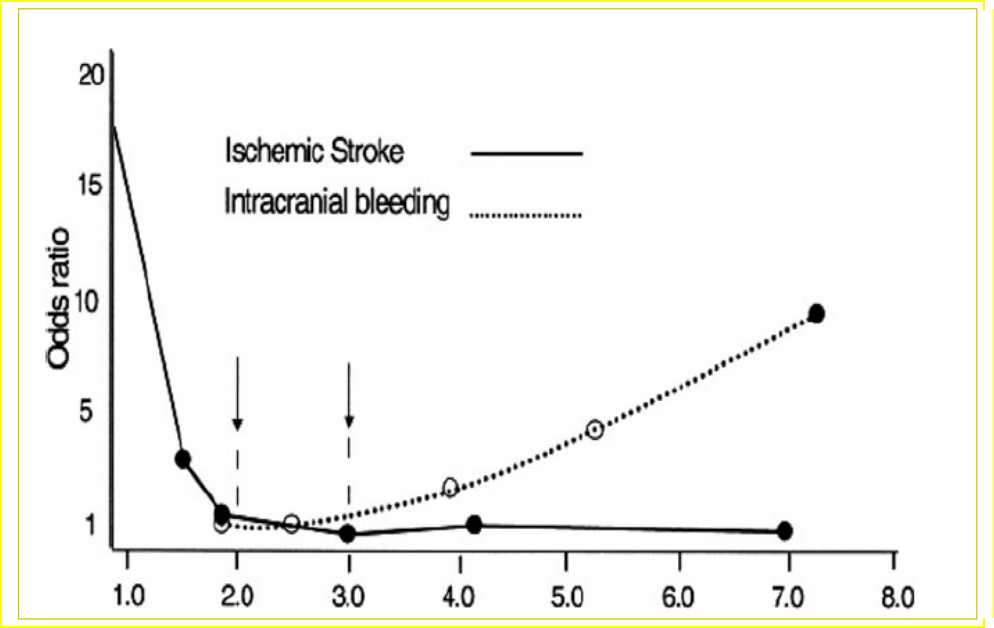
Some studies evaluated the use of ximelagatran, an OAC with protection indices and hemorrhagic complication rates similar to those of warfarin that has the advantage of not needing to monitor and control patients' INRs. However, it was found to cause severe hepatotoxicity, which has become an impediment in its clinical use (19).

The continuation of the ACTIVE study with its "A" trial evaluated the combination of aspirin and clopidogrel in comparison to aspirin alone in patients with AF and an increased risk of thromboembolism that were unable to receive a prescription for oral anticoagulants for various reasons. The combination was found to prevent thromboembolic events (especially ischemic strokes), albeit with a significant increase in the risk of hemorrhagic complications (20).

Recently, the RE-LY study (21) was published, which compared the use of the thrombin inhibitor dabigatran with warfarin in a large multicenter randomized study involving 18,113 patients with AF who had risk factors for the development of TEPs. This study showed that dabigatran (administered at a dosage of 110 mg) was associated with a rate of systemic and cerebral thromboembolic events that was similar to that observed in patients taking warfarin. Of note, there were fewer serious hemorrhagic complications observed at the 110 mg dosage. However, when the dosage of dabigatran was increased to 150 mg, lower rates of thromboembolic events were observed in the group of patients taking dabigatran (as compared to the group of patients taking warfarin), but the rate of serious hemorrhagic complications increased to a rate that was similar to that of patients taking warfarin. The announcement of these results has had a great impact to the medical community because dabigatran is the first oral drug to have a better performance than warfarin and it has the advantage of no requirement to monitor and control patients' INRs.

The intensity of anticoagulation and associated complications

INR monitoring and control in anticoagulated patients is important because patients should be anticoagulated to the degree that their risk for ischemic events is lowered, but not to the degree that increases their risk of hemorrhagic complications. An INR between 2 and 3 represents the therapeutic window in which these two objectives are obtained (22). Generally, hemorrhagic events occur with an INR of >4. Some authors report that an INR as low as 1.6 provides effective protection (23). Based on these data, other publications (2-3) recommend a goal INR of between 1.7 and 2.5 in the elderly.



Adjusted odds ratios for ischemic stroke and intracranial hemorrhage in relation to intensity of anticoagulation (based on INR) in randomized trials of antithrombotic therapy for patients with atrial fibrillation (2)

Some studies have reported a higher incidence of ischemic stroke in patients with INRs of <2. This was also associated with more severe neurological sequelae and a higher mortality rate in those patients as compared to patients with an INR of ≥2 (24-25). A later study (26) concluded that the following are risk factors for intracranial hemorrhage: advanced age, uncontrolled SAH, previous ischemic stroke, and anticoagulation intensity. Blood pressure control and a goal INR of between 2 and 2.5 seem to reduce the risk of TEP, however there is a clear need for randomized studies to better define the goal INR in these patients.

In 2006, a new analysis was done using the data published since 2003 regarding the intensity of anticoagulation (27). It concluded that anticoagulation with a goal INR of between 2 and 2.5 for patients with nonvalvular atrial fibrillation are just as effective as more intensive anticoagulation.

The Problem of the Underutilization of OACs in the Elderly

A controversial factor in TEP prophylaxis in the elderly is the risk of inducing hemorrhagic complications through the use of anticoagulant drugs, especially in patients over 75 (16, 31). On

the other hand, is it exactly this same age group that has an increased risk of ischemic stroke, or rather, this would be the group most adversely affected by not using OAC in terms of ischemic stroke risk. In reality, some studies have found an increased risk of cerebral hemorrhage in this age group (32), but it has not been proven that patients with AF should not undergo prophylaxis for that reason alone. In the end, the risk of cerebral hemorrhage corresponds to 0.6% per year, which is much smaller annual risk than that conferred by thromboembolic complications (22) if adequate prophylaxis is not prescribed.

In spite of the innumerable randomized studies that have clarified that OACs are the best choice for TEP prevention, other articles have evaluated whether or not the guidelines established by these studies were actually being followed. They have called attention to the underutilization of OACs in the elderly (29-38): just 30% of elderly patients with a formal indication for OAC use are anticoagulated, characterizing a clinical underutilization. Patients with no contraindications to OAC use do not receive the recommended therapy for more than a decade in many cases, simply because there is a fear of hemorrhagic complications from anticoagulation, in spite of the fact that the literature has already proven that the goal INR levels espoused in the literature are both safe and effective. Often, anticoagulation is only started after the first ischemic stroke.

Conclusions

The best way to prevent TEPs in patients with atrial fibrillation has been clearly defined. Of course, there are situations in which formal contraindications to OAC use exist for organic, psychosocial, and geographical reasons, which should be respected because of the implication that the risk is greater than the benefit for the elderly with AF in these cases. However, often, despite the absence of these contraindications, OAC therapy is not initiated, predisposing patients to the unnecessary risk of thromboembolic complications that can lead to irreversible neurological sequelae or death.

It is up to clinicians to try, whenever possible, to collect data on patients' medical history, to evaluate patients' organic risk factors, and to educate both patients and their family about the risks of TEPs in an attempt to establish the best therapy in a given patient. The advent of the use of new anticoagulant agents with a better safety and effectiveness profiles will make it easier to approach the issue oral anticoagulation, especially in elderly patients.

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