Antithrombotic therapy for primary and secondary prevention of Ischemic Cardioembolic CVA – Points of Interest in the Therapeutic Guidelines

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Abstract

Cerebral vascular accident (CVA) is the leading cause of death in Portugal, and as such, deserves our attention in terms of preventive care and therapy. The goal of this review is to explain the antithrombotic options to be considered in patients at risk of a cardioembolic event. The methodology used in the review process consisted of a detailed analysis of a set of papers, clinical trials and reviews, obtained through research on Medline and Google, taking in the last fifteen years of research in the field of CVA. Determining the ischemic pathogenesis of CVA, although difficult, is extremely important, as it is decisive in guiding the therapy. In thromboembolic CVA, the most frequent focus is the heart and the first step in determining the pathogenesis is to acknowledge the embolic potential of the baseline cardiopathy. Atrial fibrillation (AF) is the most frequent major risk for embolic cardiopathy. For primary prevention, patients with AF and one or more high risk factors should be treated with oral anticoagulants, and patients with low risk should be treated with antiplatelet drugs. In patients with moderate risk, the choice of therapy should consider factors such as the patient's preferences, individual bleeding risk, and the possibility of effectively monitoring the oral anticoagulant therapy. For secondary prevention, the decision regarding preventive care to be adopted should continue to be based on the most likely cause of cerebral infarction.

Key words: Cardioembolic, risk, prevention, antiplatelet, anticoagulation, cerebral infarction.

INTRODUCTION

Although the specific pathogenesis of Ischemic CVA is hard to establish, it is extremely important, as it determines the choice of therapy. Of the total cases of CVA, only 15% are hemorrhagic. The vast majority, 85%, are ischemic.

The pathogenesis in the origin of an ischemic CVA is very varied, and includes the following etiologies: 20% are secondary to atherosclerotic cerebrovascular disease, including arterial embolism, 25% are the result of penetrating artery disease, 30% are idiopathic, 20% are secondary to cardiogenic embolism, and 5% of situations have rarer etiologies, such as prothrombotic states, dissections, arteritis, etc[1].

This article focuses on the antithrombotic treatment of thromboembolic ischemic CVA dealing with the most frequent embolic focus - the heart. Among the potentially embolic heart diseases, it is important to understand which ones have higher and lower cardioembolic risk (*Table I*).

The most frequent major risk for embolic heart disease, comprising about 45% of cases, is non-valvular atrial fibrillation, therefore this review will focus mainly on this disease.

METHODS

The methodology used in the review process consists of a detailed analysis of a series of articles obtained through research on Medline and Google, taking in the last fifteen years of research on CVA. The purpose was to explain what are the antithrombotic care options for such patients.

Articles were selected within the references resulting from online research, using the following key words: "thromboembolic cerebral infarction," "cerebral ischemic CVA" and "atrial fibrillation". The selected articles were of direct interest to cardioembolic etiology.

Care was taken to include papers from Portuguese authors. Articles with repeated information, information of little relevance, or untrustworthy methodology were excluded.

ATRIAL FIBRILLATION AND CVA

Atrial fibrillation (AF) results in blood stasis with subsequent thrombus formation and embolism of the left atrial appendage. The prevalence of non-vascular AF increases with age, affecting 1% of people aged under fifty years, 5% of those aged over sixty-five, and 10% of people aged over eighty. AF itself is an independent risk factor for CVA, and for older patients it is the most important cause of cerebral infarction and the most important independent risk factor for the first event.[2,3,4]

In general, the absolute risk of CVA in patients of any age, with non-valvular AF, is 5% a year, i.e. six times higher than in patients with sinus rhythm. The potential risk is higher only in patients with a history of CVA/transient ischemic accident (TIA) which constitutes an absolute risk of recurrence of 12% a year.[3,5]

Given these facts, and taking into account that AF is associated with extensive and disabling CVA, it is of utmost importance to clinically evaluate the cardio-embolic etiology and establish an appropriate therapy. However, the medical decision is difficult and often differs from the Guidelines, since we are dealing with elderly patients with multiple risk factors and relative contraindications for anticoagulant therapy.[6,7]

PREVENTION OF CVA IN PATIENTS WITH AF

When should an embolic CVA be suspected? We should consider this etiology in patients aged under fifty or those without vascular risk factors, when there is sudden onset of the symptoms, in active patients and/or when there is rapid recovery of major neurological deficit. A suspicion of embolic incident should also be considered when a heart disease of high embolic risk is found, if there are ischemic events in more than one arterial area, or if there is no clinical or imaging evidence of arterial disease. An embolic CVA is less likely if there is evidence of lacunar syndrome, low-flow ischemia, or a history of a TIA.[3,5]

Many studies have been carried out in this context, studies SPAF (CVA Prevention in Atrial Fibrillation I, II and III) consisted of six multicentre randomized clinical studies evaluating antithrombotic therapy in primary prevention of CVA in 3950 patients with non-valvular AF.[8,9]

Two final conclusions of these studies were instrumental in guiding the treatment of these patients. Effective anticoagulation offers great benefit in pa-

Major Risk	Minor Risk
Atrial fibrillation	Uncomplicated mitral valve prolapsed
Infectious endocarditis	Mitral annular calcification
Valve Prosthesis	Patent Foramen Ovale
Recent EAM	Auricular septal aneurysm
Dilated Myocardiopathy	Aortic sclerosis
Intra cardiac tumor	
Rheumatic mitral stenosis	

tients with AF and high risk for CVA; warfarin has successfully reduced the number of primary events by 64% (CI 95% from 49% to 74%) and Acetylsalicylic Acid by only 19% (95% 2% to 34%). The second conclusion tells us that the absolute risk reduction of primary events, comparing oral anticoagulants with Acetylsalicylic Acid in non-selected patients, is less significant, and the risk/benefit ratio is obviously lower. It is therefore essential to stratify the risk of CVA in patients with non-valvular AF.[7,8,10]

Multivariate analysis of patients on Acetylsalicylic Acid included in the SPAF enabled a risk stratification scheme to be developed, with four independent risk factors for CVA: blood pressure > 160 mmHg, prior TIA/CVA, congestive heart failure in the last three months or shortening fraction ≤ 25% by transthoracic ultrasound, aged over 75 years, and female. The Atrial Fibrillation Investigators (AFI) have also identified four CVA risk factors in patients not treated with anti-platelet therapy: age (1.4 relative risk of CVA per each 10 years of age), hypertension, previous history of CVA/ TIA and diabetes mellitus. [11]

Based on earlier schemes, a classification scheme was developed in 2001, which includes $CHADS_2$ as independent risk factors for CVA: Congestive heart failure, Hypertension, Age, Diabetes and previous CVA/TIA. History of CVA/TIA counts as two points and all the other risk factors count as one point. The sum total of the scores identifies three groups of patients in terms of the risk of CVA (Table II).

Patients with previous CVA, TIA or thromboembolism are considered at high risk for recurrence and should be treated with anticoagulant. However, using CHADS2 only patients with this risk factor score two and are classified as moderate risk.[12] Due to these inac-

Risk stratification scheme of CVA in patients with non-valvular AF: CHADS$_2$

CHADS$_2$		Score	Therapy
Independent risk factors	Previous CVA/TIA	2	**Low risk** Aspirin (81-325mg)
	Arterial hypertension	1	
	Cardiac insufficiency	1	
	Diabetes	1	**Moderate risk **** Aspirin or Warfarin
	Patients ≥ 75	1	
Low risk	CHADS$_2$	0-1	**High risk** Warfarin (INR 2-3)
Moderate risk	CHADS$_2$	2-3	
High risk	CHADS$_2$	4-6	

**The decision between Warfarin and Aspirin must take into consideration the patient's preference, the individual risk of hemorrhage, and the possibility of reliably monitoring the oral anticoagulant treatment

cing the risk of CVA is similar. The start of oral anticoagulant treatment in patients with paroxysmal AF should be based not on the frequency or duration of paroxysms, but on a proper risk stratification, just as for chronic AF.[4]

The second step is the identification of any potential risk factor for bleeding during anticoagulant treatment. The third and final step is the establishment of antithrombotic treatment, anti-platelet versus anticoagulant. This choice must be based on the estimated CVA risk, and the contraindications for oral anticoagulant treatment.[10, 15, 16]

curacies, the National Institute for Clinical Excellence (NICE) has developed national clinical guidelines for treatment of AF (NICE Scheme), based on the Birmingham risk stratification scheme (Fig.1). When compared with the CHADS$_2$ scheme, it is comparable for predicting CVA and vascular events.[4]

The Guidelines of the American College of Cardiology (ACA), American Heart Association (AHA) and European Society of Cardiology (ESC) recommend oral anticoagulants for patients at high risk of CVA, patients with previous thromboembolism or rheumatic mitral stenosis, and patients with more than one moderate risk factor (age ≥ 75 years, hypertension, heart failure, left ventricular function failure and diabetes).[10] The Portuguese National Coordination for Cardiovascular Diseases recommends the use of the ACA/AHA/ESC criteria.[13]

The European CVA Association (ESO), in turn, in its 2008 recommendations for the treatment of ischemic CVA and TIA defends the use of oral anticoagulants in patients with AF who have one or more risk factors such as previous systemic embolism, age over 75 years, hypertension or poor left systolic function.[14]

Thus, regardless of the guidelines used, the first step in a patient with non-valvular AF, is to estimate the individual risk of CVA. Patients with paroxysmal AF have an annual risk of CVA that is similar to that of patients with chronic arrhythmia, therefore the effectiveness of oral anticoagulant treatment in redu-

Three other issues remain controversial, the intensity of anticoagulation, the optimal time for initiation of anticoagulation treatment after acute CVA and an interest in the association of anticoagulant and anti-platelet agents or dual anti-platelet therapy in primary prevention.[2,17, 18, 19]

The intensity of anticoagulation appears today to be more consensual, and it has been defined in the most recent ACA/AHA/ESC Guidelines that the International Normal Ratio (INR) target should be 2.5 (range: 2-3).[10] Tests WASPO (Warfarin vs. Aspirin for CVA Prevention in Octogenarians) and BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) have shown that Warfarin is safe and effective for use in elderly patients.[20,21]

However, given the fact that an INR above 1.6 appears to bring some benefit, a target value of 2.0 (target range: 1.6-2.5) was proposed by some authors in the primary prevention of patients aged over 75, with the goal of avoiding bleeding complications. However, INR factors below 2 are currently not recommended, as they are not considered to give protection against ischemic events.[3,14]

Anticoagulation therapy may be started immediately after a TIA or a minor CVA, but in case of a major CVA, with significant infarction in neuroimaging, and in situations of uncontrolled hypertension, it is advisable to delay the onset of anticoagulation by two to four weeks, However, this decision should be made
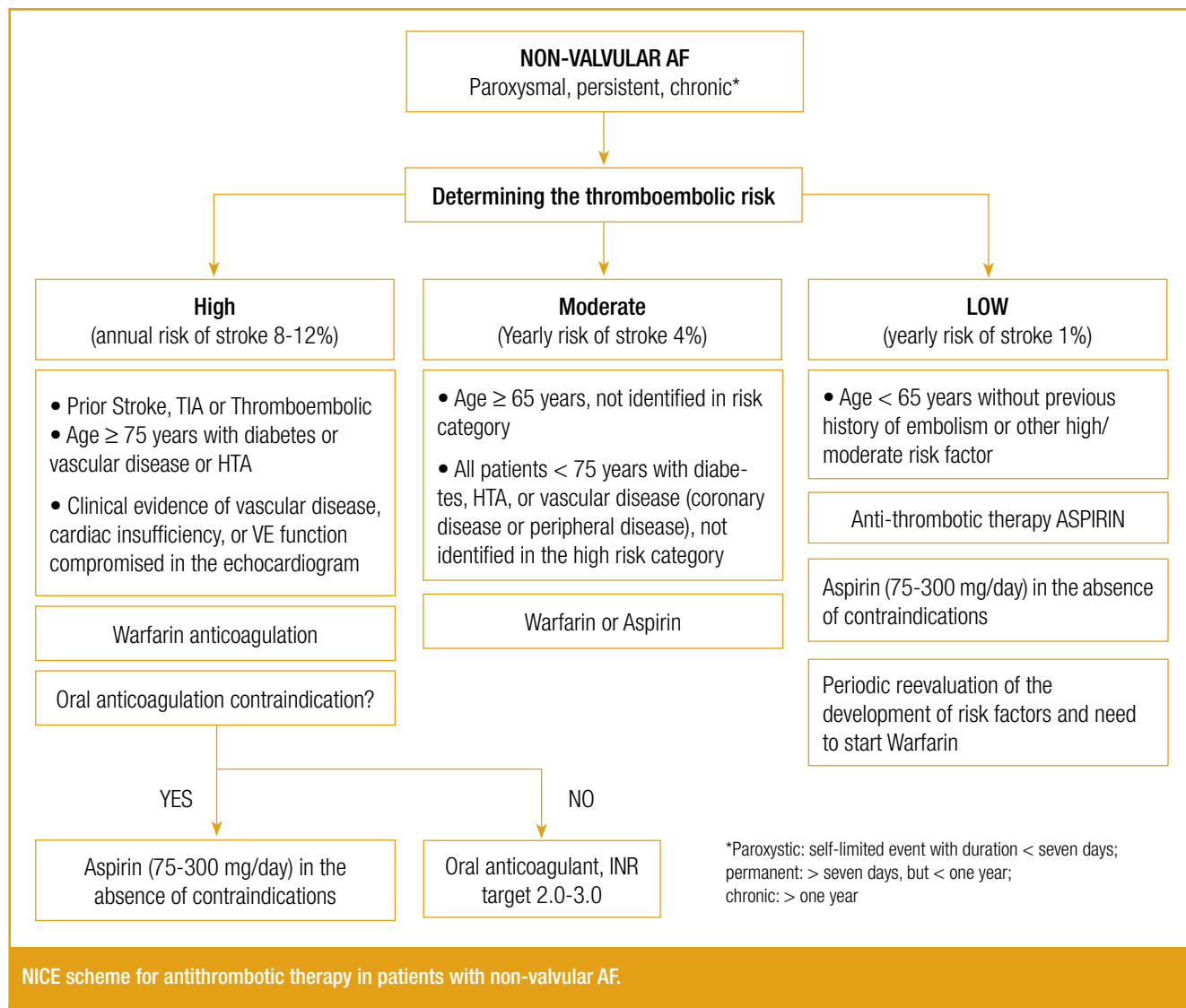
NON-VALVULAR AF
Paroxysmal, persistent, chronic*

Determining the thromboembolic risk

High (annual risk of stroke 8-12%)	**Moderate** (Yearly risk of stroke 4%)	**LOW** (yearly risk of stroke 1%)
• Prior Stroke, TIA or Thromboembolic • Age ≥ 75 years with diabetes or vascular disease or HTA • Clinical evidence of vascular disease, cardiac insufficiency, or VE function compromised in the echocardiogram	• Age ≥ 65 years, not identified in risk category • All patients < 75 years with diabetes, HTA, or vascular disease (coronary disease or peripheral disease), not identified in the high risk category	• Age < 65 years without previous history of embolism or other high/moderate risk factor
Warfarin anticoagulation	Warfarin or Aspirin	Anti-thrombotic therapy ASPIRIN
Oral anticoagulation contraindication?		Aspirin (75-300 mg/day) in the absence of contraindications
		Periodic reevaluation of the development of risk factors and need to start Warfarin

YES

NO

Aspirin (75-300 mg/day) in the absence of contraindications

Oral anticoagulant, INR target 2.0-3.0

*Paroxystic: self-limited event with duration < seven days; permanent: > seven days, but < one year; chronic: > one year

NICE scheme for antithrombotic therapy in patients with non-valvular AF.

FIG. 1

on a case-by-case basis. Anticoagulation treatment should be prescribed for the long term, or at least for three months after a cardioembolic CVA due to acute myocardial infarction.

In patients with contraindication for oral anticoagulant (co-morbid conditions such as falls, poor adherence, uncontrolled epilepsy or gastrointestinal bleeding), the recommended therapy is: low dose Aspirin for primary prevention, Aspirin (25 mg twice daily) for secondary prevention and Dipyridamole (200 mg prolonged-release twice daily). If patient is allergic to Acetylsalicylic Acid, Clopidogrel 75 mg daily.[8,10,14,15,22]

A far less consensual point is the interest on dual anti-platelet therapy in primary prevention and the combination of anticoagulant and anti-platelet agents. The vast majority of patients is indicated for the oral anticoagulant due to heart disease itself, but suffers CVA/TIA under effective oral anticoagulant treatment. Approximately one third of new CVAs in patients with AF are thrombotic and not embolic, and the oral anticoagulant appears to reduce the recurrence of such events.[23]

There is currently no data to support the use of combination of anti-platelet agents in primary preventive care for CVA in patients with AF. The ACTIVE-W found that the combination of Aspirin and Clopidogrel was less effective than Warfarin and

had a similar rate of bleeding.[24,25]

Studies involving patients in different age groups found that Aspirin should not be co-administered with Warfarin, since there was no benefit in thromboprophylaxis and it may even increase the risk of bleeding.[4] However, in studies involving patients aged over 75 with a higher frequency of CVAs and bleeding complications, the moderate combination of anti-platelet and anticoagulation (INR 1.25-2.0) significantly reduced the risk of new events and fatal bleeding complications. The study NASPEAF (National Study for Prevention of Embolism in Atrial Fibrillation) sub-studies used Acenocoumarol as the anticoagulant and Triflusal as the antiplatelet agent.[26,27,28,29]

Treatment of patients with AF who have had recurrent vascular events under antiplatelet therapy due to oral anticoagulant contraindication remains uncertain. Alternative causes of CVA must be sought, and control of CVA risk factors is especially important in these patients. Several strategies can be considered: not altering the therapy, switching to another antiplatelet drug, or adding another antiplatelet drug. In patients under oral anticoagulant suffering recurrent CVAs, the therapeutic guidelines are equally uncertain.[13,14]

CONCLUSIONS

Primary prevention of CVA in patients with AF should involve the treatment of hypertension and dyslipidemia and the control of other risk factors, as well as stratification of the CVA risk. Risk stratification should be performed using the various schemes available, of which the $CHADS_2$ appears to be the most practical, or by the independent risk factors listed in the ACA/AHA/ESC Guidelines. Patients with high risk should be treated with oral anticoagulants, and patients with low risk should be treated with Acetylsalicylic Acid. In patients with moderate risk, the therapeutic choice must consider factors such as patient preferences, the individual risk of hemorrhage and the possibility of effectively monitoring the oral anticoagulant therapy.[4,10,12,14] Patients with AF with a longstanding or recent history of CVA or TIA, should receive secondary preventive care with Warfarin. [3,10,16] The association of anticoagulant with an INR score two and Triflusal 600 mg per day anti-platelet may be an alternative in patients over 75 years of age, with significant reduction in the risk of new events and less tendency to cause bleeding complications.[27,28] It

seems that the therapeutic option for secondary preventive care for patients on Warfarin, in therapeutic doses, may be influenced by the most likely cause of CVA and patient age. Further studies are needed to validate this hypothesis. ◼

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