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REVIEW ARTICLE

Antithrombotic therapy in nonvalvular atrial fibrillation: A narrative review

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Abstract Atrial fibrillation (AF) is an important and potentially modifiable cause of stroke. It has been known since 1989 that oral anticoagulant drugs, such as warfarin, lead to a dramatic decrease in stroke associated with AF. The best risk-benefit ratio is obtained with intensity of oral anticoagulant treatment for an INR of 2–3, even in the elderly. Given the risks of anticoagulant therapy, including bleeding, individual thromboembolic risk must be assessed in patients with AF. In 2009, dabigatran was shown to be a reasonable alternative to vitamin K antagonists, establishing itself as a major alternative to warfarin in AF patients. Rivaroxaban and apixaban have subsequently also been shown to be alternatives to warfarin. When there are contraindications to vitamin K antagonists, antiplatelet agents can produce a therapeutic effect, although much less than oral anticoagulants. Apixaban may be a better alternative to aspirin in this setting. Patients with low-risk atrial fibrillation (no risk factors) have not been the subjects of specific clinical trials. It is unclear what would be the best therapeutic choice for these patients.

PALAVRAS-CHAVE
Fibrilação auricular;
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Dabigatrano;
Rivaroxabano;
Apixabano

Terapêutica anti-trombótica na fibrilação auricular não-valvular: uma revisão narrativa

Resumo A fibrilação auricular (FA) é uma causa importante e potencialmente modificável do acidente vascular cerebral. Desde 1989 que se encontra demonstrado que o uso de anticoagulantes orais, como a varfarina, se associa a uma redução dramática da incidência de acidente vascular cerebral associado a FA. A intensidade da anticoagulação oral com uma melhor relação risco-benefício é obtida com um INR de 2-3, mesmo no paciente idoso. Tendo em consideração os riscos da anticoagulação oral, incluindo as hemorragias, é necessário estimar o

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risco tromboembólico individual nos doentes com FA. Em 2009, o dabigatrano mostrou ser uma alternativa razoável aos antagonistas da vitamina K – vindo a estabelecer-se como uma alternativa importante à varfarina em doentes com FA. Foi subsequentemente demonstrado que quer o rivaroxabano quer o apixabano têm um estatuto semelhante ao dabigatrano, enquanto alternativas importantes à varfarina. Quando existam contra-indicações à terapêutica com antagonistas da vitamina K, os antiplaquetários podem produzir um efeito terapêutico, sem dúvida um efeito muito menos importante do que os anticoagulantes orais. O apixabano poderá ser uma alternativa preferível à aspirina neste contexto. Os doentes com FA de ''baixo risco'' (sem factores de risco) não foram estudados em ensaios clínicos levados a cabo especificamente para esta situação. É pouco claro qual é a melhor alternativa terapêutica nestes doentes.

Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation, resulting in deterioration of atrial function. According to the 2010 ESC guidelines,[1] AF is considered to be paroxysmal if it ends spontaneously or persistent if it lasts more than seven days or requires termination by cardioversion. According to the same document, ''long-standing persistent AF has lasted for $\geq$1 year when it is decided to adopt a rhythm control strategy'', and ''permanent AF is said to exist when the presence of the arrhythmia is accepted by the patient (and physician)''.[1]

AF is the most common sustained arrhythmia, being responsible for one-third of hospitalizations related to cardiac rhythm disturbances.[2] In the last 20 years, admissions due to AF have risen by 60%, which may not only be the result of changes in admission thresholds or clinical practices, but could also reflect a genuine increase in the population incidence.[3] In a large European study (the Rotterdam study), the overall prevalence was 5.5%, rising from 0.7% in those aged 55–59 years to 17.8% in those aged 85 and over.[4] In the FAMA study, the overall prevalence of AF in 10 447 patients aged 40 or over was 2.5%; male gender, increasing age, body mass index, hypertension and lack of physical exercise were noted to influence the prevalence of AF.[5]

AF is associated with increased long-term risk of stroke. According to the Framingham study,[6] the two-year age-adjusted incidence of stroke among patients with AF averages 5%, approximately 5 times that of people without AF. The estimated relative risk (RR) of stroke for patients with AF ranges from 2.6 in those in the 7th decade of life to 4.5 in the 9th decade. Furthermore, the attributable risk of stroke for AF ranges from 1.5% in patients aged 50–59 years to 23.5% in those aged between 80 and 89 years.[6]

The formation of thrombi due to blood stasis in the left atrial appendage is believed to be a common initial step for cardioembolism in patients with AF[7]; many other independent risk factors are linked to an increased risk of stroke in these patients, the most consistent being a previous history of stroke, thromboembolism or transient ischemic attack (TIA), diabetes, hypertension and age.[8] Other factors are congestive heart failure (CHF) and coronary artery disease (CAD).[9]

As a result of the high morbidity and mortality associated with AF, it is imperative to prevent its complications, especially thromboembolic phenomena. The aim of this narrative review is to analyze existing data regarding the efficacy and the risk-benefit ratio of the various antithrombotic modalities available for the prevention of the major vascular complications related to nonvalvular AF, particularly stroke and systemic embolism. All secondary cases of AF – in the context of myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism or acute lung disease – were excluded from this review, since in these cases AF may cease to exist with management of the underlying condition.

Due to the heterogeneity of the articles of interest (in the number of patients enrolled, inclusion and exclusion criteria, length of follow-up and drugs under evaluation), an individual description of major clinical trials was performed.

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Clinical trials on antithrombotic therapy in atrial fibrillation

Studies involving warfarin or other oral anticoagulants

AFASAK I (1989)

In the first Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study (AFASAK I), 1007 patients aged 18 or over with chronic nonvalvular AF documented by electrocardiogram (ECG) were randomized to openly receive warfarin (international normalized ratio [INR] 2.8–4.2, *n*=335), or, blindly, aspirin (75 mg/day, *n*=336) or placebo (*n*=336).[10] The following were exclusion criteria: cerebrovascular events within the past month, previous anticoagulant therapy for more than six months, hypertension above 180/100 mmHg, valvular heart disease, valve replacement, or current therapy or contraindication to aspirin or warfarin treatment. The primary endpoint was stroke, TIA or systemic embolism. The secondary event was death.

The mean follow-up was two years. In the warfarin group, compared to the aspirin group and placebo, there was a