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REVIEW ARTICLE

Ana Faustino*, Luís Paiva, Rui Providência, Romeu Cação, Marco Costa, António Leitão-Marques

Serviço de Cardiologia, Centro Hospitalar e Universitário de Coimbra – Centro Hospitalar de Coimbra, Coimbra, Portugal

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KEYWORDS

Atrial fibrillation; Thromboembolism; Stroke; Left atrial appendage; Anticoagulation; Cardiac implant **Abstract** Atrial fibrillation is a common arrhythmia in clinical practice. It is associated with high morbidity and mortality due to its thromboembolic potential, which makes thromboembolic prevention particularly important. Warfarin has been the first-line therapy for this purpose, but it has various limitations and is often contraindicated or underutilized. The fact that thrombi are frequently located in the left atrial appendage in atrial fibrillation led to the development of percutaneous closure for thromboembolic prevention. This article examines the current evidence on percutaneous closure of the left atrial appendage by reviewing the results of the numerous clinical trials on the technique.

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PALAVRAS-CHAVE

Fibrilhação auricular; Tromboembolismo; Acidente vascular cerebral; Apêndice auricular esquerdo; Anticoagulação oral; Implante cardíaco

Encerramento percutâneo do apêndice auricular esquerdo para profilaxia de tromboembolismo na fibrilhação auricular

Resumo A fibrilhação auricular é uma arritmia frequente na prática clínica. Associa-se à morbilidade e à mortalidade elevadas, em virtude do seu potencial tromboembólico, o que confere especial relevância à profilaxia do tromboembolismo. Para este efeito, a varfarina tem sido a terapêutica de primeira linha, no entanto, associa-se a inúmeras limitações, que a tornam contraindicada ou sub-utilizada. A localização frequente no apêndice auricular esquerdo dos trombos formados na fibrilhação auricular conduziu a que o seu encerramento percutâneo fosse desenvolvido para profilaxia do tromboembolismo. Este artigo pretende fazer um enquadramento da evidência atual para o encerramento percutâneo do apêndice auricular esquerdo, através de uma revisão e atualização dos resultados dos inúmeros estudos realizados até ao momento.

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* Corresponding author.

E-mail address: anacatarina.faustino@gmail.com (A. Faustino).

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Introduction

Atrial fibrillation (AF) is a common arrhythmia with high morbidity and mortality due to its thromboembolic potential. Warfarin has been the first-line therapy for thromboembolic prevention, but it has various contraindications and limitations. Thrombi in AF form mainly in the left atrial appendage (LAA), and so closure of the LAA is considered an alternative to warfarin therapy.

Prevalence of atrial fibrillation

AF is the most common cardiac arrhythmia in clinical practice. Its prevalence in Portugal is 2.5% in those aged 40 or over according to the FAMA study.¹ The figure in the general population is 1-2%, rising with age; prevalence has increased significantly over time and is predicted to double in the next 50 years.²

The importance of thromboembolism in atrial fibrillation

The risk of stroke is five times higher in those with AF than in those in sinus rhythm.^{2,3} The large size of the thrombi that cause these strokes means that their consequences tend to be more severe than from other sources of cerebral thrombi.^{2,4-6}

Chronic anticoagulation with warfarin

Oral anticoagulation with warfarin remains the first-line therapy to prevent thromboembolic events in AF. It is indicated in all patients with CHADS₂ or CHA₂DS₂-VASC score \geq 2, and should also be considered with a score of 1.² Its efficacy has been demonstrated in numerous randomized clinical trials, which have shown that with a target international normalized ratio (INR) of 2–3, relative risk for stroke is reduced by 60–73%.^{2,4–9} Its superiority over aspirin (reduction of 20%^{2,7}), combined aspirin and clopidogrel, and a single antiplatelet drug plus low-dose warfarin,^{2,10,11} is well established.

However, warfarin is contraindicated in 14–44% of patients at risk of stroke.¹² Even among eligible patients, only 54% are anticoagulated, for a variety of reasons, the most important being bleeding risk; others include a narrow therapeutic window and the sensitivity of its pharmacokinetics to a range of foods and other drugs, which necessitate frequent laboratory testing and the patient's cooperation. The risk of trauma, access to INR monitoring, clinicians' wariness, and patient preferences can also make warfarin therapy impractical.⁴ Anticoagulation is thus often inadequate, and INR values are within the therapeutic window in only 50–68% of tests.⁹

New oral anticoagulants

New anticoagulants have been developed as alternatives to warfarin for thromboembolic prevention in AF. There are two main classes: direct thrombin inhibitors such as dabigatran, and factor Xa inhibitors such as rivaroxaban,

apixaban, edoxaban and betrixaban. They all have advantages over warfarin including a wider therapeutic window, fewer interactions with foods, and no need for laboratory monitoring.² Only dabigatran (the RE-LY study¹³). rivaroxaban (ROCKET-AF¹⁴) and apixaban (ARISTOTLE¹⁵) have demonstrated non-inferiority to warfarin in thromboembolic prevention in AF, and only the first two have been approved by the US Food and Drug Administration (FDA) for this purpose.¹⁶ The latest guidelines for the management of atrial fibrillation of the European Society of Cardiology consider dabigatran an alternative in patients at high embolic risk if warfarin is contraindicated or impractical.² The latest Canadian Cardiovascular Society guidelines also recommend the use of dabigatran rather than warfarin in AF patients with indication for oral anticoagulation.¹⁷

However, these drugs are expensive for chronic therapy, carry a significant risk of bleeding, and do not have an established antidote, all which are obstacles to their use in many patients. Studies on these new anticoagulants have also shown significant rates of discontinuation of therapy, mainly due to intolerance or adverse effects, reaching 25.3% in patients taking apixaban (vs. 27.5% for those taking warfarin) in the ARISTOTLE trial,¹⁵ but higher than seen for warfarin in the RE-LY¹³ (21% for dabigatran vs. 17%) and ROCKET-AF¹⁴ (23.7% for rivaroxaban vs. 22.2%) trials.

The importance of the left atrial appendage in thromboembolism

The LAA is an embryonic remnant of the left atrium (LA) consisting of a long tubular body with walls as little as 1 mm thick, usually multilobulated and trabeculated, that communicates with the LA through an oval orifice.^{18,19} It is generally thought to have a role in regulating body volume via physiological mechanisms that include the production of 30% of atrial natriuretic peptide, regulation of thirst, and modulation of the volume/pressure ratio and LA compliance, and hence cardiac output.^{20–22}

The LAA is also the most common site of intracardiac thrombi in AF (98%), as demonstrated in autopsy studies, by transesophageal echocardiography (TEE) and by direct intraoperative inspection.^{11,12,18,19} It is more frequently the site of thrombi in non-valvular (90%) than valvular AF (57%),^{12,18,19} and in patients with previous ischemic stroke.²⁰

In the light of these facts, exclusion of the LAA from the circulation was seen as an alternative to pharmacological anticoagulation to prevent thromboembolism in AF. Different methods have been developed, some more invasive than others. 12,13

Surgical exclusion of the LAA

The first attempt to surgically exclude the LAA, during mitral valve surgery, was described in the 1930s.⁵ The LAAOS study, the first randomized trial of surgical LAA occlusion, in patients referred for coronary bypass surgery at risk for AF or ischemic stroke, concluded that surgical exclusion of

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