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Review

Oral anticoagulation in chronic kidney disease with atrial fibrillation☆

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ABSTRACT

Atrial fibrillation is a common finding in patients with chronic kidney disease (CKD), which increases markedly the embolism risk. The $CHADS_2$ and HAS-BLED scales, used in the general population to assess the risk/benefit of oral anticoagulation (OAC), underestimate respectively the risk of embolism and haemorrhage in CKD, making it difficult to decide whether to use OAC or not. Based on the available evidence, it seems indicated to use OAC in stage 3 CKD, while it is controversial in advanced stages. New OAC such as dabigatran and rivaroxaban have been approved in stage 3 CKD but their role is still somewhat uncertain.

Anticoagulación oral en la enfermedad renal crónica con fibrilación auricular

Palabras clave:
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RESUMEN

La presencia de fibrilación auricular en pacientes con enfermedad renal crónica (ERC) resulta un hallazgo frecuente que aumenta de forma considerable el riesgo embólico. Las escalas $CHADS_2$ y HAS-BLED, utilizadas en la población general para valorar el riesgo/beneficio de la anticoagulación oral (ACO), infraestiman, respectivamente, los riegos de embolia y hemorragia en la ERC, haciendo complicada la indicación de ACO en estos pacientes. Con la evidencia disponible, parece indicada la ACO en ERC estadio 3, siendo controvertido su uso en estadios más avanzados. Si bien resultan prometedores los nuevos ACO, dabigatrán y rivaroxaban, aprobados para ERC estadio 3, su papel esta aún por esclarecer.

Introduction

There is a close, bidirectional relation between chronic kidney disease (CKD) and cardiovascular disease which, in recent years, has led to CKD being considered an independent global marker of cardiovascular risk and to the adoption of the term "cardiorenal syndrome".[1] Cardiovascular disease is present even in the initial stages of kidney disease, favouring its perpetuation and progression, and representing the main cause of morbidity and mortality of patients with kidney disease.[2] Atrial fibrillation (AF) is one of the conditions linked to kidney disease. Until recently, AF had been forgotten in the literature on patients with kidney disease. However, once again, interest has been aroused due to its higher prevalence in the population, its damaging consequences, and the therapeutic challenge it entails—particularly regarding the need for anticoagulation to prevent systemic embolic episodes and strokes.

Epidemiology

AF is particularly common in patients with CKD. In patients on haemodialysis, the prevalence of AF ranges between 7% and 20%; in long-term haemodialysis it reaches 27%.[3,4] This disparity in prevalence may be due to the characteristics of the populations included in studies, as well as to the methods of detecting AF and its classification as paroxysmal or persistent/permanent. Moreover, frequency is closely related to age and increases by up to 37% in patients aged 71–80 years.[5] These figures are at least 2–3 times higher than AF rates in the general population.

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The increased arrhythmic load is not limited to patients on haemodialysis. Recently, several studies have found increased AF incidence and prevalence (9–21%) in large numbers of CKD patients who were not yet receiving dialysis, with progressive increases of both in inverse proportion to the decrease in glomerular filtration rate.[6–9]

In contrast, epidemiological data from cardiology research shows that up to one third of AF patients have some level of renal dysfunction.[10] Even among patients participating in randomised trials of new anticoagulant drugs—all of whom meet exclusion criteria based on renal function—some 15–21% presented creatinine clearance of 30–50 ml/min.

Consequences of atrial fibrillation

AF is the main cause of ischaemic stroke secondary to multiple physiopathological mechanisms and not exclusively secondary to major left atrial blood stasis.[11] These strokes caused by AF tend to be more severe in relation to residual incapacity, as well as short- and medium-term mortality.[12] In patients with kidney disease, the stroke rate is, by nature, higher in all stages of the disease. Both AF and CKD are "hypercoagulation" states, with stroke rates in end-stage patients that are four- to tenfold greater than in similar populations without CKD, with substantial disparities between the different series published.[13]

However, it is worth mentioning that in moderate- or advanced-stage CKD, AF is an independent risk factor for stroke; in end-stage CKD and in patients receiving haemodialysis, the relative increase is not consistent in all series, probably due to the multi-cause nature of stroke in these patients, and a reduction in the specific impact of AF.[14–16]

Although the present review focusses on embolic episodes and their treatment, we should say that while the major complication of AF is stroke, its consequences also involve reduced tolerance to exercise, reduced quality of life, an increased rate of hospitalisation, episodes of heart failure, and increased left ventricular function impairment, which independently predicts mortality and is twice as common in patients with AF by comparison with equivalent populations without arrhythmia.[17]

Therefore, in CKD patients, AF has a damaging effect on kidney function itself[18] and worsens prognosis by comparison with the general population without CKD. AF doubles short- and medium-term mortality in patients receiving dialysis,[4,19–21] although controversy remains as to whether AF in patients with kidney disease is an independent predictor of mortality or merely a marker of poor underlying cardiovascular condition.

In practical terms, these data oblige us to optimise, as far as possible, the treatment of patients with kidney disease and AF. This includes the management of associated vascular risk factors, the assessment of antiarrhythmic drugs in those who need rhythm control, recording ventricular frequency, heart failure symptoms and, above all, preventing stroke and embolic episodes.

Assessment of the embolic/haemorrhagic risk

The stratification of embolic and haemorrhagic risk is the first step in treating AF.

Embolic risk

The $CHADS_2$ scale assigns one point for each of the following items: congestive heart failure, high blood pressure, age >75 years, and diabetes mellitus; it assigns 2 points for a history of stroke or transient ischaemic attack. It has been fully validated and shows a 2% increase in the rate of stroke for each one-point increase in score (from 1.9% for a $CHADS_2$ score of one point to 18.2% for a score of 6 points). The most recent European guidelines for AF treatment included the CHA_2DS_2-VAS_c scale (Table 1). This is similar to the previous version but assigns 2 points for age >75 years, one point for age 65–74 years, and one point for vascular disease (myocardial infarction, peripheral arterial disease, aortic plaque). The guidelines recommend its use to define at-risk patients with a $CHADS_2$ score under 2 points.[17]

Table 1
Embolic risk estimation: CHA_2DS_2-VAS_C.

	Situation	Points
C	Congestive heart failure or left ventricular systolic dysfunction	1
H	High blood pressure	1
A_2	Age > 75 years	2
D	Diabetes mellitus	1
S_2	Stroke, TIA or thromboembolism	2
V	Vascular disease	1
A	Age = 65–74 years	1
S_C	Female gender	1

TIA: transient ischaemic attack.
Source: Camm et al.[44].

However, the value of these scores in patients with kidney disease is controversial since the risk of stroke may be underestimated. The highest possible $CHADS_2$ score (6 points) implies an annual risk of 18.2% whereas some series of patients with CKD present stroke rates of up to 24%, despite the absence of some of the risk factors analysed. Once again, these higher figures may be due to the occurrence of multi-cause strokes in patients with kidney disease who have a baseline state of hypercoagulation that neither $CHADS_2$ nor CHA_2DS_2-VAS_c takes into account. Despite the underestimation of individual stroke risk, in patients receiving haemodialysis, the application of these scores leads to the indication for oral anticoagulation (OAC) in most cases, though the efficiency of anticoagulation with vitamin K antagonists (VKA) has not been demonstrated in this population. We will analyse this further below. In this context, we should mention that the $CHADS_2$ scale has not been validated in patients receiving dialysis and that in developing CHA_2DS_2-VAS_c, only 5.8% of the patients included had CKD, and no indication was given as to how many of these were receiving dialysis.[22]

Haemorrhagic risk

The potential benefit of ischaemic stroke prevention in patients with AF must be compared to the inherent risk of haemorrhage associated with the anticoagulant treatment. VKA anticoagulation is a therapeutic dilemma in patients with CKD. These patients consistently present increased risk of major haemorrhage while receiving VKA treatment.[16,23] This is even more evident in patients receiving haemodialysis given their greater baseline risk of multi-cause bleeding.[22]

To date, 4 stratification scores for haemorrhagic risk while receiving VKA treatment have been published and 3 of them include kidney function as a risk factor. None has been adequately validated for clinical use. European and Canadian guidelines[22] recommend the HAS-BLED score (Table 2) to predict haemorrhagic risk. This is based on the presence of high blood pressure, hepatic or kidney function abnormalities, prior stroke or bleeding, international normalised ratio (INR) lability, age >65 years, and alcohol consumption or concomitant use of drugs that favour bleeding. It assigns a major haemorrhage risk ranging from 1% (score 0–1) to 12.5% (score 5). The HAS-BLED score includes CKD—even though it was present in only a few of the study patients—but it seems to underestimate the haemorrhage rate, given the increased baseline risk. Once again, this is particularly evident in patients receiving haemodialysis in