

Atrial fibrillation in advanced renal failure: are there alternative solutions to warfarin-dicumarol?

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Patients with atrial fibrillation (AF) and chronic renal failure (CRF) represent a growing population in epidemiological terms since both conditions increase with advancing age. The association of AF and CRF is burdened with a poor prognosis and with a high risk of adverse events, both ischaemic and haemorrhagic. Oral anticoagulant therapy, in these patients, is more problematic, especially due to the concomitant increased risk of bleeding. The use of direct oral anticoagulants (DOACs) in patients with non-severe renal insufficiency appears to be safe and effective. Since all currently available DOACs are at least partially eliminated by the kidney (dabigatran is the direct anticoagulant with the highest rate of renal elimination, approximately 80%), periodic monitoring of renal function is recommended to evaluate possible need for dosage adjustment. In patients with advanced renal insufficiency, the use of DOAC appears controversial, given the small number of clinical studies that have tested its efficacy and safety. It is known, however, that oral anticoagulation therapy with vitamin K antagonists (VKAs) is associated with an increase in nephropathy and renal-vascular calcification. From this point of view, therapy with DOAC could be more advantageous than VKAs. Data from clinical studies would seem to show that the use of dabigatran and rivaroxaban in these patients may lead to a reduction in the inevitable deterioration of renal function.

Introduction

Atrial fibrillation (AF) is the most frequent heart rhythm disorder, with an incidence that progressively increases with increasing age and is associated with an increased risk of morbidity and hospitalization.¹ However, the most alarming complications, also negatively impacting the quality of life and social costs, are ischaemic stroke and systemic embolism (SE). The risk of these events is closely related to the patient's risk profile which can be estimated with the aid of numerical 'scores' (CHA₂DS₂-VASc), but fundamentally, it is significantly reduced by treatment with oral anticoagulants (OACs); however, treatment with OAC inevitably leads to an increased risk of bleeding events.²

Current guidelines recommend therapy with OAC for the prevention of stroke in patients with AF and CHA₂DS₂-VASc score ≥ 2 in men and ≥ 3 in women, and should be considered with a score of one in men and two in women.³

The OACs historically administered to patients with AF have been vitamin K inhibitors [warfarin and acenocoumarol (vitamin K antagonist, VKA)] with variable daily dosage based on international normalized ratio values. Research progression has led to the availability of four direct oral anticoagulants (DOACs)⁴⁻⁷: one factor IIa inhibitor (dabigatran) and three direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), whose therapeutic efficacy does not require monitoring. Each DOAC was compared with VKAs in an *ad hoc* randomized controlled trial (RCT) study in patients with non-valvular AF; in a meta-analysis of these four RCTs, the use of DOACs was associated with a significant 19% reduction in stroke or SE, a similar reduction in stroke, a non-significant reduction in major bleeding, an

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increase in gastrointestinal bleeding, but above all a significant reduction in total mortality (10%) and a halving of intracranial haemorrhages.⁸

Based on current evidence, in patients with non-valvular AF (excluding mechanical valve prostheses or moderate to severe mitral stenosis) for stroke prevention, the use of DOACs should be preferred over VKAs with the highest recommendation class.

Atrial fibrillation and chronic renal failure

Among the factors that increase the likelihood of developing AF, in addition to age, arterial hypertension, diabetes mellitus, ischaemic heart disease, is also included chronic renal failure (CRF), and CRF patients are frequently affected with FA.⁹ In patients with AF, the presence of CRF is associated with an increased risk of stroke¹⁰; however, the use of OAC in this population is more difficult, due to the concomitant increased bleeding risk, so much so that a clear clinical benefit is still under discussion.¹¹

Although there are different methods to classify the degree of CRF, the creatinine clearance (CrCl) calculated with the Cockcroft-Gault formula is certainly the one that has been most used in the trials that have evaluated OAC therapy.

The results of a meta-analysis of 11 patient cohorts (6 retrospective and 5 prospective) that included nearly 50 000 patients showed that treatment with VKA in patients with AF and non-terminal CRF was associated with a reduction stroke/embolism rate without leading to a significant increase in bleeding; on the contrary, in patients with terminal CRF, the effect on ischaemic events and mortality was neutral, with a significant increase (12%) in bleeding events.¹² Another more recent meta-analysis confirmed that in patients with terminal CRF and AF, treatment with warfarin is associated with a neutral effect on ischaemic stroke, mortality, and major bleeding but with a significant increase in haemorrhagic strokes.¹³

The use of direct anticoagulants in patients with chronic kidney disease

Although VKAs have historically been the drugs of choice in patients with AF and advanced chronic kidney disease, there is evidence that their use in this context may not be the ideal solution. Adverse events such as renal-vascular calcifications¹⁴ and worsening of renal function have been reported.^{15,16} The use of DOACs has therefore begun to be considered also in patients with advanced degrees of renal dysfunction. All currently available DOACs are at least partially eliminated by the kidney. Dabigatran is the direct anticoagulant with the highest rate of renal elimination (about 80%), followed by edoxaban (about 50%); the renal elimination of rivaroxaban and apixaban is, conversely, less prevailing (35% and 27%, respectively).¹⁷ Currently, little evidence is available on the use of DOACs in patients with severe renal impairment. With the exception of a small group of patients from the ARISTOTLE study, all major DOAC pivotal trials excluded patients with CrCl less than 30 mL/min. In view of this, in Europe dabigatran is

contraindicated in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min; for rivaroxaban, apixaban and edoxaban, on the other hand, a reduction in dosage is anticipated if the eGFR is between 15 and 29 mL/min, and are contraindicated for eGFR <15 mL/min. Based on pharmacokinetic studies, the US drug agency (FDA) has approved the use of reduced-dose dabigatran (75 mg b.i.d.) in patients with an eGFR between 15 and 29 mL/min. Since CrCl is a dynamic parameter, it is evident that the periodic re-evaluation of renal function can be of practical importance in the management of these patients. In this regard, the practical guide of the European Heart Rhythm Association (EHRA) of 2021 recommends monitoring CrCl at least annually or with a frequency in months equal to the CrCl value divided by 10 in the case of an estimated eGFR <60 mL/min.¹⁷ However, it is necessary to stress that chronic kidney disease should be kept separate from acute kidney injury. In the latter condition, the estimate of CrCl can, in fact, underestimate the degree of renal dysfunction; the dosage and therapy with DOACs should therefore be carefully reassessed until an interruption of the therapy is considered which, depending on the clinical context, could be replaced with a parenteral anticoagulant agent.

Real-world data have shown how the deterioration of renal function, quite common in AF patients treated with DOAC, documenting an eGFR reduction of at least 30% in one in four patients at 2 years, can be influenced by the type of DOAC administered. In particular, dabigatran and rivaroxaban therapy appears to be associated with a lower risk of worsening renal function in these patients.¹⁸

The use of DOACs in patients with terminal CRF on haemodialysis

The available data on the use of DOACs in patients with terminal CRF or haemodialysis derive from small studies, mainly of pharmacokinetics.

A 4-h dialysis session in patients with terminal CRF and treated with apixaban 5 mg × 2 per day resulted in drug exposure almost comparable to that of healthy volunteers.¹⁹ However, in another pharmacokinetic study in dialysis patients, the apixaban 5 mg × 2 dose was associated with plasma levels well above the therapeutic range, while the 2.5 mg × 2 dose gave more acceptable results.²⁰ The RENAL-AF study presented at the American College of Cardiology congress in 2019 did not demonstrate differences in efficacy and safety between apixaban and warfarin in patients with AF and dialysis; however, its premature discontinuation with a sample of 154 patients compared to the 760 expected make the results inconclusive.²¹

The pharmacokinetic and pharmacodynamics profile of rivaroxaban 15 mg/day was similar in patients on dialysis compared to patients with moderate-severe CRF.²²

The results of two recent meta-analyses, although performed on observational studies that mostly compared apixaban or rivaroxaban vs. warfarin in patients on dialysis, did not reveal significant differences in terms of efficacy and safety between the two treatments.^{23,24}

Conclusions

Based on current evidence, the balance between the risks and benefits of anticoagulant therapy in patients with AF and advanced chronic kidney disease is not yet fully established. Although the drugs historically prescribed in this context are VKAs, there is evidence that their use may not be the ideal solution and DOACs could represent an alternative in this clinical context. The evidence on their use in patients with terminal CRF or haemodialysis treatment, although promising, is however still limited and the European regulatory agency contraindicates its use in this type of patient. Mainly on the basis of pharmacokinetic studies, the US Food and Drug Administration has provided for the use of apixaban and rivaroxaban also in patients treated with haemodialysis, opening on the possibility of using DOACs in this context; On the contrary, in the absence of strong evidence in this regard, the European regulatory body has not approved the use of any DOAC in this category of patients.

However, further studies will be necessary to clarify the indication for anticoagulant therapy in patients with AF and terminal CRF and to evaluate the risk-benefit profile of the various anticoagulant drugs available, also considering therapeutic alternatives such as percutaneous closure of the left auricle.

Conflict of interest: none declared.

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