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EDITORIAL

THE CHALLENGES OF USING DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Direct oral anticoagulants (DOAC) are undeniably a vital pillar of antithrombotic therapy. Dabigatran is a direct thrombin inhibitor that acts by preventing the conversion of fibrinogen to fibrin. Apixaban, betrixaban, edoxaban and rivaroxaban are selective factor Xa inhibitors. Since the first market launch of a DOAC 15 years ago, the number of indications has greatly expanded, based on their superior efficacy and safety in many clinical scenarios compared to classical vitamin K antagonists (VKAs). The indications include prevention of stroke and systemic embolism in patients with atrial fibrillation (AF); prevention of major cardiovascular events in patients with chronic coronary artery disease or peripheral artery disease; treatment of deep vein thrombosis and pulmonary embolism; prevention of recurrent venous thromboembolism (VTE); and prevention of VTE after total knee or hip replacement, or in hospitalized acutely ill medical patients (1). DOACs have several advantages over VKA, such as rapid onset and offset of action, limited food and drug interactions and a wider therapeutic window. They have a stable and predictable effect that allows the administration of fixed doses and does not require monitoring of the anticoagulant effect.

There is a solid bidirectional link between cardiovascular and kidney disease. Not only do they share the same risk factors, such as age, hypertension, dyslipidemia, diabetes, and obesity, but these two diseases are connected by pathophysiological links that allow them to increase each other's incidence and rate of progression in a downward spiral ending in premature heart failure, end-stage renal disease (ESRD) and death.

Individuals with chronic kidney disease (CKD) have an increased risk of thrombotic events, both arterial and venous, with up to half of patients with stage 4-5 CKD being affected during their lifetime. The prothrombotic state is the consequence of complex imbalances affecting the vascular endothelium, platelets and plasma factors of coagulation and fibrinolysis. Toxins related to renal disease decrease the expression and limit the activation of endothelial NO synthase, thereby reducing NO bioavailability and NO-mediated endothelial vasodilation (2). The endothelium becomes activated and expresses adhesion molecules, including the von Willebrand factor, which is responsible for the adhesion of platelets to the endothelium as the first step in generating thrombosis. The functional changes occurring in platelets transform their phenotype into a preactivated one (3). At the level of the damaged vessel wall, the tissue factor is exposed and initiates coagulation and thrombin generation. CKD patients have increased levels of factors V and VIII and reduced levels of antithrombin III, proteins C and S, which favor thrombosis (4). Impaired fibrinolysis is another important factor. The most important change is the increase in fibrinogen and PAI-1 levels. Moreover, fibrin clots

have a dense structure and are less permeable to the action of fibrinolytic enzymes, therefore more difficult to lyse.

CKD patients have a cluster of traditional cardiovascular risk factors, accelerated atherosclerosis and a double prevalence of atrial fibrillation compared to the general population (5). In addition, factors deriving from the presence of renal disease, such as volume overload, albuminuria, abnormal calcium-phosphate metabolism and anemia, also contribute to very high cardiovascular risk. Thus, patients with CKD not only have an increased risk of acute coronary syndromes (ACS) and peripheral arterial disease of the lower limbs but also of ischemic stroke. The greater the decline in renal function and the greater the albuminuria are, the more severe the acute arterial vascular events and the worse the prognosis. The risk of stroke is 5-30 times higher in CKD patients compared to the general population, especially in those on dialysis, and fatal in almost 90% of cases. CKD doubles the mortality rate among ACS patients and ranks third after cardiogenic shock and congestive heart failure as a predictor of mortality (6). A moderate and severe decrease in renal function causes a 2.5 times and 5.5 times increase in the risk of VTE, respectively, compared to normal renal function (7). In addition, the risk of VTE recurrence is 5.3 times higher in CKD patients compared to individuals with normal renal function (8). In dialysis patients - higher in those with hemodialysis than with peritoneal dialysis - the major risk is to develop pulmonary embolism, a risk that is double that of the population without CKD (9).

Patients with CKD not only have an increased risk of thrombosis, but also an increased risk of bleeding. Platelet hypo reactivity is the main contributor. Uremic toxins interfere with platelet-vessel wall interaction, platelet adhesion, aggregation and release of alpha granules, leading to a hemorrhagic phenotype (3). The risk of bleeding increases gradually as kidney function declines. Patients with ESRD have a threefold increased risk of bleeding compared to those without CKD. One in seven patients with stage 5 CKD will experience a major bleed within 3 years of starting dialysis. Of all bleeding sites, hemorrhagic stroke and upper gastrointestinal bleeding are particularly common (10).

As expected, the risk of bleeding increases with the addition of antithrombotic drugs, either antiplatelet or anticoagulant or combination therapy as needed in patients with AF and ACS treated by percutaneous coronary intervention (PCI). Moreover, the difficulty of antithrombotic therapy also lies in the fact that patients with advanced disease, stages 4-5 CKD, have generally been excluded from large, randomized trials or have been underrepresented. When choosing a DOAC for a patient with renal failure, a number of aspects must be considered, such as the severity of renal function decline, the type of DOAC, and the indication (AF or VTE; prevention or therapy).

All DOACs have a renal route of elimination, but there is great variability among them: dabigatran (80%), edoxaban (50%), rivaroxaban (35%), apixaban (27%) and betrixaban (7%). Thus, assessment of renal function is mandatory before initiation of any DOAC and periodically throughout treatment. Moderate or severe renal impairment may contraindicate the use of DOAC or require dose reduction in patients with AF. Dabigatran requires dose reduction at CrCl 30-49ml/min and is contraindicated at CrCl less than 30 ml/min. CrCl is

an essential reference point for establishing the indication for dose reduction in the remaining DOACs. Caution is advised when using low doses of apixaban, edoxaban and rivaroxaban in patients with CrCl 15-29ml/min. In a pooled analysis of patients with AF and stages 3-4 CKD of the pivotal trials of DOAC, all-cause mortality and the rate of all stroke and systemic embolism were slightly reduced by DOAC compared with warfarin (11). In addition, patients receiving a DOAC had less major bleeding than patients treated with VKA, particularly those with stage 4 CKD. Compared with warfarin, patients receiving a DOAC had a trend toward a reduction of intracranial hemorrhage, but slightly more gastrointestinal bleeding. To summarize, DOACs are preferred over VKAs in stages 1-4 CKD, except for dabigatran, which cannot be used in stage 4 CKD (12).

To date, all DOACs have been contraindicated at CrCl less than 15 ml/min (13). The 2020 ESC guidelines for the diagnosis and management of atrial fibrillation state that all DOACs are contraindicated in AF patients on dialysis. However, off-label use has been reported. Increased risk of bleeding was found in patients receiving dabigatran and rivaroxaban (14), but not apixaban (15). Furthermore, dose reduction was considered unnecessary because the composite outcome, including stroke/systemic embolism, major bleeding, and death, was more favorable with a dose of 5 mg bid compared with a lower dose of 2.5 mg bid, especially in terms of stroke prevention (16). New data has recently become available. The RENAL-AF trial published its results in December 2022 and reported that among patients with AF and ESRD on hemodialysis, apixaban treatment had similar rates of bleeding and stroke as warfarin (17). Of note, 71% of patients in this study received apixaban 5 mg bid. Although enrollment challenges led to the premature termination of the study and there was inadequate power to draw any conclusion, one finding should be highlighted, namely, that patients on hemodialysis experienced clinically relevant bleeding approximately ten times more frequently than thrombotic events (stroke cerebrovascular or systemic embolism).

A large meta-analysis showed that DOACs have similar efficacy and better safety than warfarin in preventing VTE recurrence across the spectrum of CKD severity (18). Although rates of intracranial bleeding were similar, DOAC users had fewer clinically relevant major and non-major bleeds than patients receiving VKAs. A systematic review focusing on the prevention of recurrent VTE in CKD patients reinforces these findings (19). Of note, one study showed better efficacy of dabigatran compared to warfarin in elderly patients with moderate renal impairment. DOACs and warfarin similarly reduced the risk of recurrent VTE and had a similar overall risk of bleeding. However, the risk of overall major bleeding from DOACs increased with decreasing renal function, except with apixaban. Additionally, in dialysis patients, apixaban had less overall bleeding compared to warfarin. Based on pharmacokinetic and pharmacodynamics studies, apixaban and rivaroxaban were recently approved by the Food and Drug Administration (FDA) for use in ESRD patients. Furthermore, in patients with VTE and ESRD, a retrospective analysis showed that apixaban has similar efficacy and better safety than warfarin. The incidence of major bleeding, including intracranial and gastrointestinal bleeding, was significantly lower in DOAC users (20).

Another element that differentiates DOACs is the binding to plasma proteins and implicitly the possibility that the drug is dialyzable. Protein binding is strongest for rivaroxaban (92-95%) which is not dialyzable, followed by apixaban (87%), betrixaban (60%), edoxaban (55%) which are partially dialyzable and finally dabigatran (35%), which is the most dialyzable.

A debate is related to the best method of evaluating the renal function, in order to adjust the dose or establish the contraindication for DOAC administration. In patients receiving apixaban, the parameter that defines the renal function is the value of serum creatinine. In patients receiving dabigatran, edoxaban or rivaroxaban, creatinine clearance is used to estimate renal function. The FDA, the highest authority providing guidance to the pharmaceutical industry, recommends that dose adjustment in patients with renal impairment be based on CrCl estimates and explicitly states that the Cockcroft-Gault formula should be used. Therefore, the pivotal trials with DOACs estimated renal function according to this recommendation (21-24). Because the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas estimate renal function more accurately than the Cockcroft-Gault formula and are widely implemented in current practice, dose mismatches may occur. It was recently shown that approximately 40% of AF patients would have required DOAC dose adjustment if either the MDRD or CKD-EPI formulas had been used instead of the Cockcroft-Gault formula (25). The consequences of this reclassification would have been 5 times increase in the risk of thrombotic events and a numerical increase in major bleeding events. This situation must be known and recognized as very important. Until the academic community and the pharmaceutical industry provide guidance for dose adjustments based on MDRD or CKD-EPI-estimated renal function, DOAC dose adjustments should continue to be made on the basis of renal function estimated by the formula used in the pivotal trials to ensure reproducibility in terms of efficacy and safety of DOAC use.

In the absence of CKD, renal function should be assessed at least annually, and for patients over 75-80 years of age, at least once every 6 months. When CKD is present (CrCl $\leq$ 60 mL/min), the interval between assessments is calculated according to the formula: the number of months = ClCr/10. In addition, renal function will be assessed whenever there is an acute event that may suddenly alter renal function.

We can conclude that the evidence of efficiency and safety of DOAC accumulated in recent years represents a strong ally in the reliable management of anticoagulant therapy in this fragile category of patients, which combines at the same time an increased thrombotic risk, but also a hemorrhagic one. There is increasing evidence that DOACs can be used across the spectrum of CKD.

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