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REVIEW

Atrial fibrillation in kidney transplant recipients: is there a place for the novel drugs?

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ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia of high clinical importance, occurring in 2% of the general population and in 19–24% in patients with chronic kidney disease. It is a well-known risk factor for cardiovascular morbidity and mortality. Kidney transplant recipients with a history of AF were associated with significantly higher rate of ischaemic strokes, graft failure and post-transplant mortality. AF occurs in over 7% of kidney transplant recipients in the first 3 years after transplantation and is associated with reduced graft and patient survival. The incidence of stroke in patients after kidney transplantation (KTx) is higher than the general population, but markedly lower than those on dialysis. Oral anticoagulation (OAC) therapy is recommended in AF patients at high risk of stroke. There are no randomized studies assessing OAC in patients after KTx and there are no specific recommendations and guidelines on therapeutic strategies in these patients. KTx recipients are a vulnerable population, exposed to variations in renal function, being at higher risk of bleeding and thrombotic complications, with possible interactions with immunosuppression. Surely, there is a place for novel oral anticoagulants (NOACs) in this group of patients as long as the summary of product characteristics is followed, as they are a valuable anticoagulation therapy. On one hand, they are at least as effective as warfarin; on the other hand NOACs are safer, especially when it comes to intracranial haemorrhages. However, NOACs seem to be underused in this population as they are excreted via kidney, may interact with immunosuppressive therapy and physicians need more experience and confidence in their administration. Percutaneous left atrial appendage occlusion procedure may also be considered as an opportunity for this group of patients, in particular in the presence of contraindications to anticoagulation.

Keywords: anticoagulation, atrial fibrillation, kidney transplantation, NOACs, warfarin

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia of high clinical importance, occurring in 2% of the general population, and is a well-known risk factor for cardiovascular morbidity and mortality [1]. Patients with chronic kidney disease (CKD) have increased risk for cardiac arrhythmias. Studies published in the last few years demonstrated that AF frequently occurs in patients with CKD and ranges from 19% to 24% rising to 27% in patients with end-stage renal disease (ESRD) [2, 3]. The prevalence of AF among this large population of patients with impairment of kidney function is 2- to 3-fold higher than in the general population [4–7]. Moreover, several studies have implicated AF as a contributing factor in CKD and cardiovascular events [2, 8]. Possible mechanisms that may explain the high rate of AF among CKD patients are

excessive inflammation, left ventricular hypertrophy, large left atrial and activation of the renin–angiotensin–aldosterone system [5, 9–13].

Kidney transplantation (KTx) is the preferred treatment for patients with ESRD in terms of life expectancy and quality of life [14, 15]. Cardiovascular disease is the leading cause of death following KTx, accounting for 30–50% of mortality [16, 17]. The annual risk of a cardiovascular death is 3.5–5% in recipients of KTx, which is 50-fold higher than in the general population [18–20]. Nevertheless, KTx reduces long-term cardiovascular mortality when compared with chronic dialysis patients [21, 22].

PATIENTS PREVIOUSLY DIAGNOSED WITH AF

History of AF was reported in approximately 6% of patients undergoing KTx and was associated with poor post-transplant outcomes [23]. In large population of US kidney transplant recipients, history of AF was associated with significantly higher rates of ischaemic stroke, graft failure and post-transplant mortality [23]. Patients with baseline AF had a 37% higher risk of post-transplant stroke than patients without AF. During 5-year follow-up 40.6% of AF patients died and risk of death was 2.4-fold higher than in patients without arrhythmia [23]. In the study of Delville *et al.* [24] on 244 potential kidney allograft recipients older than 50 years, repolarization abnormalities were reported in 19 (7.8%) patients, conduction anomalies in 14 (5.8%) and arrhythmia in 9 (3.7%).

INCIDENCE OF AF AFTER KTx

KTx recipients present not only with various traditional risk factors of AF, such as diabetes, obesity, hypertension, smoking and coronary artery disease [25], but also with more specific risk factors related to ESRD, such as anaemia, endothelial dysfunction, calcaemia and phosphataemia imbalance [14, 26–29]. AF occurs in over 7% of kidney transplant recipients in the first 3 years after transplantation and is associated with reduced graft and patient survival [30]. The incidence of AF is higher in the peri-transplant period, associated probably with surgical stress, anaesthesia and excess catecholamine production [31]. Following KTx (after approximately 17 months), AF declines below the prevalence recorded in ESRD patients on the transplant waiting list [32]. A possible explanation may be the regression of left ventricular hypertrophy over the first 2 years after transplantation [30]. In the study of Delville *et al.* [24] a 12 month, follow-up was available for all 244 patients. Overall, 38 (15.5%) renal transplant recipients had a cardiovascular event during the first year post-transplantation with AF reported in 13 (5.3%) of them.

In the single-centre study in Italy, AF episodes in the post-operative period were observed in 6% of the patients and 32% of these patients had two or more AF episodes [33]. Factors associated with incidence of AF were older age, male, history of hypertension and coronary artery disease [33]. Age was the strongest AF risk factor and a cutoff value of 53 years was identified, which maximizes predictive sensitivity and specificity [33]. Abbott *et al.* [34] in the cohort study of 39 628 KTx recipients estimated the rate of new-onset AF after transplantation at approximately 6 events per 1000 person-years and found that AF was independently associated with a 34% increase in all-cause mortality [34]. Among KTx recipients older age, ESRD due to hypertension, higher body mass index, used of cyclosporine (compared with tacrolimus), delayed graft function, acute rejection and graft loss were independently associated with an increased risk of hospitalization for AF [34]. In another report of 31 136 patients new-onset AF after transplantation was 3.6% and 7.6% at 12 and 36 months, respectively [30]. Post-transplant risk factors for AF were age >60 years, male gender, white, ESRD due to hypertension, dialysis duration before transplantation and coronary artery disease. New-onset AF was independently associated with death, death-censored graft failure and all-cause graft failure [30]. In addition, in a small study on 38 older patients (69.8 ± 3.8 years) compared with the 49 younger kidney recipients (mean age 47.8 ± 11.9 years old), the incidence of coronary heart disease, chronic heart failure and AF was higher in the older patients (28.2% versus 8.2%, respectively; $P < 011$), stressing the importance of the age factor [35].

STROKE IN KTx RECIPIENTS

The incidence of stroke in patients after KTx is higher than the general population, but markedly lower than those on dialysis. Stroke in transplant recipients shares similar traditional risk factors observed in the whole population, but it remains unclear whether reversal of modifiable factors can reduce the risk of stroke. Cerebrovascular disease diagnosis after transplantation is associated with increased mortality.

In a large study of 29 614 KTx recipients investigators observed that new-onset cerebrovascular events [ischaemic stroke, transient ischaemic attacks (TIAs) and haemorrhagic stroke] after transplantation are common, affecting nearly 7% of recipients with functional grafts by 3 years after transplantation [36]. The authors of this study describe the incidence of 24.6 cerebrovascular events per 1000 person-years in those who receive KTx compared with 45.6 events per 1000 patient-years in dialysis patients. Furthermore, KTx predicts a 34% reduction in risk of subsequent cerebrovascular events compared with remaining on the transplant waiting list, whereas risk for cerebrovascular disease increased >150% after graft failure. What is more, cerebrovascular events after transplantation independently predicted increased risk for mortality, with the strongest risk conferred by haemorrhagic events. In another study of 1633 adult patients who received a kidney allograft, stroke or TIA were observed in nearly 4% of the patients during a 4 year follow-up. In the study cohort, history of AF and diabetes were detected as independent predictors of cerebrovascular events after KTx [37]. In another study of 956 patients with a functioning kidney transplant stroke incidence was 5.96 per 1000 patient-years and the majority (84.6%) of events were ischaemic [38]. Factors associated with stroke were history of cerebrovascular events, AF, diabetes, age, higher systolic blood pressure and haemoglobin concentration. In the analysis of time to ischaemic stroke in those with and without AF there was a significant association between presence of AF and stroke [38].

ANTICOAGULATION THERAPY

Oral anticoagulation (OAC) therapy is indicated in the general population with AF for ischaemic stroke and systemic thromboembolism prevention [1]. According to European Society of Cardiology (ESC) guidelines, CHA_2-DS_2-VASc and HAS-BLED score is obligatory to assess stroke and bleeding risk, respectively.

The CHA_2-DS_2-VASc score [congestive heart failure/left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 years and sex category (female)] is used for risk stratification of ischaemic stroke in patients with non-valvular AF. The ESC guidelines for the management of AF recommend the CHA_2-DS_2-VASc score for decision-making whether to use thromboprophylaxis in everyday clinical practice [39].

Bleeding risk is assessed using scores that are mainly aimed not at disqualifying patients from anticoagulant therapy, but primarily at supporting dosing selection. The most commonly used HAS-BLED score contains clinical bleeding risk factors and abnormal laboratory test results (such as uncontrolled hypertension, abnormal renal function, abnormal liver function, prior history of stroke, prior major bleeding or predisposition to bleeding, labile international normalized ratio, age ≥65 years, prior alcohol or drug usage history, medication usage predisposing to bleeding: antiplatelet agents, nonsteroidal anti-inflammatory drugs). It has been developed based on data from Vitamin K antagonists (VKAs)-treated patients [40]. In this HAS-BLED score abnormal renal function was defined as undergoing permanent dialysis, having prior transplant or having serum creatinine >2.26 mg/dL or >200 μmol/L. Depending on the score, the annual bleeding risk amounts to 0.6% up to even 19.6%. HAS-BLED score usability with respect to patients treated with novel oral anticoagulants (NOACs) is widely accepted, although other scores in this setting are also suggested [1, 41].

OAC is recommended in AF patients at high risk of stroke (CHA_2-DS2-VASc score ≥2 in men and ≥3 in women) and should be considered if there is a score of 1 in men and 2 in women [1]. However, patients with severe renal impairment were excluded from randomized controlled trials on AF. Moreover, there are no randomized studies assessing OAC in patients after KTx and there are no specific recommendations and guidelines on therapeutic strategies in these patients. KTx recipients are a vulnerable population, exposed to variations in renal function, being at higher risk of bleeding and thrombotic complications, with possible interactions with immunosuppression.

The prescription of OAC therapy should be guided by the estimated glomerular filtration rate (eGFR) of the graft and potential pharmacokinetic interactions of OAC with immunosuppressive agents should be considered [1]. In general, eGFR is considered the best index of graft function and also a predictor of graft and patient survival, but no formula has been consistently shown to be superior to any other formula in patients after KTx [42–49]. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the care of KTx recipients recommends measuring serum creatinine and estimating GFR using one of several formulas validated for adults at least: daily for 7 days or until hospital discharge, two to three times per week for Weeks 2–4, weekly for Months 2 and 3, every 2 weeks for Months 4–6, monthly for Months 7–12 and every 2–3 months, thereafter [50].

It should be noticed that KTx improves renal function and transfer patients from Stage 5 in the KDIGO classification (eGFR <15 mL/min) to predominantly Stage 3, rarely to Stage 1 or 2 [32].

VKAs have historically been the standard of care for long-term OAC in the general population and solid organ recipients. In a contemporary cohort of US kidney transplant recipients with newly diagnosed AF, warfarin use was associated with a small non-significant reduction in the composite outcome of death, stroke or gastrointestinal bleed [51]. The authors stressed that kidney transplant recipients with AF were less likely to receive warfarin than has been reported in the general population [52]. Despite the guidelines recommendation that individuals with AF and a $CHADS_2$ score ≥2, in the absence of a contraindication, should be treated with OACs [1], in their study, just 24.6% and 30.8% of study subjects with a $CHADS_2$ score ≥2 and ≥4, respectively, received warfarin treatment following a diagnosis of AF. They suggested that doctors' unwillingness to anticoagulate kidney allograft recipients with AF may reflect not only the lack of available evidence for warfarin therapy in this vulnerable population, but also some 'spill-over' concern about enhanced risk of bleeding reported in haemodialysed subjects [53, 54]. The limitation of this study included lack of data on transplant function, which could be a factor affecting the decision to initiate warfarin in a kidney allograft recipients with AF. Moreover, there was no information on whether AF was transient (perhaps related to surgery or inter-current illness) or sustained, which could also potentially influence the decision to treat with warfarin.

NOACs including dabigatran, rivaroxaban, apixaban and edoxaban offer new therapeutic approaches in AF. They have a significantly lower risk of intracranial bleeding compared with warfarin [55, 56].

In the case of NOACs there is no need to control anticoagulant effects on a regular basis. This is considered to be one of the main benefits of this group of drugs. Nevertheless in urgent situations such as bleeding or the need for an emergency operation, identification of direct oral anticoagulant and anticoagulation assessment might be necessary [57].

The most characteristic feature is the very significant prolongation of thrombin time (TT) with dabigatran. Normal TT confirms that dabigatran is not present in the bloodstream. Activated factor X inhibitors do not have any effect on TT assay. Prolongation of the prothrombin time is the most pronounced with rivaroxaban, whereas it is it is activated partial thrombin time (APTT) prolongation with dabigatran, although the prolongation depends on the reagent used and on individual characteristics. None of the screening plasma coagulation tests can be used for laboratory NOACs activity monitoring with the aim of adjusting the dose to ensure that a therapeutic effect is obtained. The tests do not provide clear evidence that NOAC concentration in a given patient is correct. Different results of screening coagulation tests in various patients receiving the same dose of the same NOAC have been observed. Results of

more precise tests such as dilute thrombin time (dTT) and ecarin clotting time better correlate with dabigatran than APTT and TT tests; however, their availability is limited. Anti-Xa activity assay, performed differently for individual activated factor X inhibitors, is used for precise assessment of their concentrations [58, 59]. However, since therapeutic range of the NOACs is largely unknown dose adjustment is inadvisable.

Treatment with NOACs in patients with severe renal impairment (eGFR <30 mL/min) is approved in Europe but it is not recommended according to the European Guidelines because there are no effectiveness and safety data in this population [1]. In the previous review available data on treatment of AF in patients with CKD were discussed with particular attention being paid to NOACs therapy [60]. In kidney allograft recipients, we have to bear in mind the potential interactions with immunosuppressive therapy. However, there is a very limited data on the effect of NOACs in KTx recipients on immunosuppression. NOACs and the calcineurin inhibitors, tacrolimus and cyclosporine, share certain metabolic pathways that could raise concerns over potential bidirectional drug interactions [61]. According to the Practical Guide on NOACs by Heidbuchel *et al.* [62] dabigatran is not recommended for use with cyclosporine and tacrolimus. The treatment with immunosuppressive drugs raises the concentration of edoxaban by 73%. There are no data yet on apixaban and rivaroxaban [62]. In real life some patients who are treated with NOACs should have more frequent assessment of calcineurin inhibitor level, particularly in the initiation of the treatment to adjust the dose appropriately. Moreover, all NOACs are eliminated partially via the kidneys: dabigatran 80%, rivaroxaban 35%, apixaban 27% and edoxaban 50% [62]. Therefore, graft function should be monitored closely to make dose adjustment when needed. At the time of publication, idarucizumab, a dabigatran-specific reversal agent, is the only available antidote for NOACs. Studies are underway with respect to factor Xa inhibitors antidote (andexanet alfa) and a universal antidote acting on NOACs, heparins and fondaparinux (ciraparantag). Idarucizumab should be used in patients with life-threatening bleeding or before urgent major surgeries [63–66].

PERCUTANEOUS LEFT ATRIAL APPENDAGE CLOSURE—POSSIBLE STROKE PREVENTION

The number of patients with absolute or relative contraindications to OAC was estimated at 13–20% of the whole population of patients with AF [67, 68]. Patients with advanced kidney disease are at high thromboembolic risk but unfortunately also at high bleeding risk [69]. Severe kidney failure, being usually one of the exclusion criteria in large clinical trials, makes the decision to use anticoagulation more difficult.

Al-Saady *et al.* [70] described left atrial appendage (LAA) as a place of formation of thrombus causing over 90% of cardioembolic events in patients with non-valvular AF. The European Heart Rhythm Association Survey listed end-stage renal failure with co-existing high risk in CHA_2-DS_2-VASc score as one of the indications to percutaneous LAA occlusion (LAAO) [71]. A published registry study evaluating the safety and efficacy of percutaneous LAAO among patients with CKD showed similar

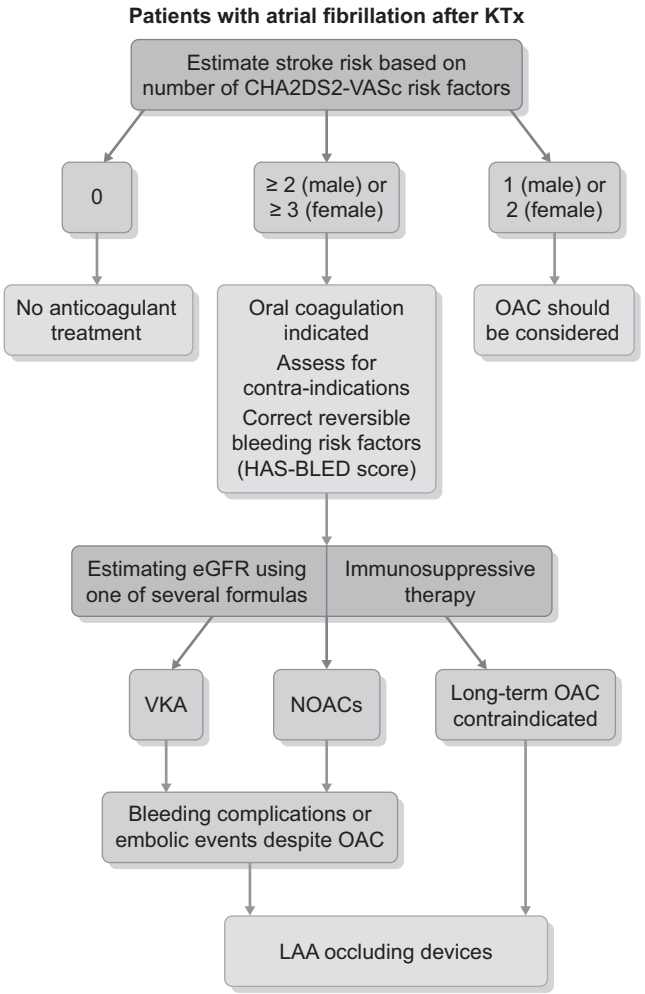

FIGURE 1: Proposed algorithm of AF management in KTx.

safety among patients with CKD compared with patients with normal renal function. An important reduction of stroke and TIA rate and also bleeding rate was observed when compared with expected annual risk [72].

Nevertheless, it should be noted that percutaneous LAAO has some clinical requirements. A transoesophageal echocardiogram is necessary to assess the LAA anatomy and to exclude the presence of thrombus in LAA. Dual antiplatelet therapy, which is also associated with increased risk of bleeding, is indicated after the procedure. Its duration has not been clearly defined, ranging from 1 to 6 months [73].

SUMMARY

AF in kidney allograft recipients is associated with a significantly higher rate of ischaemic strokes, graft failure and post-transplant mortality. Prophylactic antithrombotic treatment reduces mortality, the rate of stroke and systemic emboli. There are no specific guidelines available for use of anticoagulation in these patients. More studies are needed to assess the clinical efficacy and safety of NOACs in patients after KTx. A proposed algorithm for AF management in KTx is presented (Figure 1). Surely, there is a place for NOACs in this group of patients, as long as the summary of product characteristics is followed, as they are a valuable

anticoagulation therapy. On one hand they are at least as effective as warfarin, and on the other hand NOACs are safer especially when it comes to intracranial haemorrhages. However, NOACs seem to be underused in this population as they are excreted via kidney, may interact with immunosuppressive therapy and physicians need more experience and confidence in their administration. Percutaneous LAAO procedure may also be considered as an opportunity for this group of patients, in particular in the presence of contraindications to anticoagulation.

CONFLICT OF INTEREST STATEMENT

A.T.-K. has given lectures and consultations for Boehringer Ingelheim and consultation for Bayer. The remaining authors declare no conflict of interest.

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