Can direct oral anticoagulants be used in kidney transplant recipients?

DOI:
10.1111/ctr.14474

Document Version
Accepted author manuscript

Can Direct Oral Anticoagulants be used in Kidney Transplant Recipients?

Kathrine Parker[1,2], Janette Chu[3], Muir Morton[1], Shiv Bhutani[1], Michael Picton[1], Sandip Mitra[1,4], Jecko Thachil[5].

1. Manchester Institute of Nephrology and Transplantation, Manchester University NHS Foundation Trust, Oxford Road, Manchester, United Kingdom, M13 9WL
2. The University of Manchester, Division of pharmacy and optometry, School of health sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester, United Kingdom, M13 9PT
3. Department of Pharmacy, Manchester University NHS Foundation Trust, Oxford Road, Manchester, United Kingdom, M13 9WL
4. The University of Manchester, Division of cardiovascular sciences, School of medical sciences, Manchester, United Kingdom, M13 9NT
5. Department of Haematology, Manchester University NHS Foundation Trust, Oxford Road, Manchester, United Kingdom, M13 9WL

Running head: DOACs in kidney transplantation

Corresponding Author:

Kathrine Parker MPharm MFRPS II MSc(dist) NMP NIHR clinical doctoral fellow

Manchester Institute of Nephrology and Transplantation

Manchester University NHS Foundation Trust

Oxford Road

Manchester

M13 9WL

E-mail: Kathrine.parker@mft.nhs.uk

Telephone: 07743859741

Number of Tables: 4

Word Count (excluding tables, figures, references, abstract): 4653

Abstract count: 200

Parker K, Chu J, Bhutani S, Picton M, Mitra S, Morton M, Thachil J. Can Direct Oral Anticoagulants be used in Kidney Transplant Recipients? Clin. Transplant

Abstract

Background

Kidney transplant recipients(KTRs) are at increased risk of venous thromboembolism (VTE) and atrial fibrillation(AF). Direct oral anticoagulants (DOACs) have shown important advantages over vitamin K antagonists; however, in KTRs concerns regarding interactions and use in severe kidney disease may limit their use. This evaluation describes a large UK kidney transplant center's experience of DOACs in KTRs with CrCl>15ml/min.

Methods

Electronic records were reviewed for all adult KTRs at Manchester University Foundation Trust Hospitals taking DOACs between January 2018 and October 2020 with VTE or AF. The primary outcome was trough and peak DOAC levels within the expected reference ranges and secondary outcomes included bleeding and thrombotic events.

Results

In thirty-one KTRs taking DOACS, eight patients had a CrCl<30ml/min. Overall 94% (62/66) of DOAC levels were within the recommended ranges. There were no thrombotic events and four bleeding events (two major and two clinically relevant non-major bleeds). The overall bleeding rate was 6.9 per 100 patient-years at risk.

Conclusions

There was no evidence of a significant interaction of apixaban or rivaroxaban with CNIs based on expected DOAC and CNI levels. Their use was found to be safe and effective with no VTE events and bleeding episodes similar to published trial data.

Keywords: Direct oral anticoagulants (DOACS), Kidney transplant, Anticoagulation, Atrial fibrillation, Venous thromboembolism

Introduction

Kidney transplant recipients (KTRs) are at increased risk of developing venous thromboembolism (VTE)[1]. This risk is highest within the first 12months of undergoing transplant surgery but the risk remains elevated[1] with the incidence of new VTE reported in up to 9% of KTRs with a median time to presentation of 17months post-transplant[2]. The reasons for this are not fully explained by traditional risk factors such as cancer or hospitalisation but are likely to be multifactorial and include renal impairment[2].

Atrial fibrillation (AF) is also relatively common in kidney transplant recipients. Approximately 6% of patients undergoing kidney transplant have pre-existing AF with the incidence of AF occurring post-transplant reported to be 3.6% at 12months and 7.3% at 3 years[3]. AF in transplant recipients is associated with both worse patient and graft survival[4]. Kidney transplant recipients have traditional risk factors for AF development such as diabetes, hypertension and coronary artery disease but also specific factors related to end-stage renal disease such as endothelial dysfunction, calcium and phosphate homeostasis abnormalities[5, 6]. Around 17 months post-transplant AF prevalence declines to below that of those on the transplant waiting list. This has been suggested to be related to a regression of left ventricular hypertrophy in the initial two years post-transplant[6].

Traditionally vitamin K antagonists (VKAs) have been the mainstay of treatment for VTE and AF but in recent years direct oral anticoagulants (DOACs) have shown important advances over vitamin K antagonists (VKAs) with their rapid onset of action, lack of monitoring and ease of dosing. They have been shown to have similar efficacy to VKAs but with a reduced risk of intracranial bleeding including in those with chronic kidney disease (CKD)[7-9].

However in kidney transplant recipients there is still some hesitation about the use of DOACs due to potential interactions with calcineurin inhibitors (CNIs) and their reliance on renal excretion which may be problematic in this population[10]. The CNIs tacrolimus and ciclosporin are moderate/strong inhibitors of P-glycoprotein (P-gp) and the metabolic enzyme CYP3A4[11]. Rivaroxaban and apixaban have some reliance on CYP3A4 metabolism, approximately 18% and 25% respectively[11], and inhibition of this enzyme may result in an increase of their exposure. All of the DOACs are substrates of P-glycoprotein (P-gp) an efflux transporter found in the luminal wall of the small intestinal, apical membrane of hepatocytes and proximal epithelium of renal tubules. Inhibition of this P-gp transport pathway has the potential for increased DOAC plasma levels. Concerns relating to increased exposure to DOACs would be an increase in the risk of bleeding. Currently the European Heart Rhythm Association guidelines suggest to consider avoiding concomitant use of tacrolimus with DOACS, although there is limited data to support these recommendations[12].

KTRs usually have some degree of renal dysfunction after kidney transplantation. This is relevant in the present context since renal excretion plays a role in the clearance of the DOACs ranging from 27% with apixaban to 80% of dabigatran[13]. In patients with moderate to severe renal impairment (creatinine clearance (CrCl)<30ml/min) there is limited outcome data with the use of DOACs due to exclusion from the randomised trials[14-17]. Although the use of DOAC level monitoring is not routine practice, situations where patients have multiple factors affecting the pharmacokinetics of DOACs have been suggested as a reason to undertake monitoring[18].

Here we describe an evaluation of a large UK kidney transplant centres experience of the use of DOACs in transplant recipients with CrCl$\geq$15ml/min where DOAC level monitoring and review of bleeding and thrombotic outcomes were undertaken to assess efficacy and safety.

Methods

Study design

This is a single centre retrospective evaluation to examine the safety of using DOACs in a large kidney transplant centre. All adult kidney transplant recipients at Manchester University NHS Foundation trust, UK who were taking DOACs in the timeframe January 2018 to October 2020 were included.

The indications for DOACs were limited to treatment of venous thromboembolism (VTE) and non-valvular atrial fibrillation (AF). The diagnosis of deep vein thrombosis (DVT) was by either venography or compression ultrasound and pulmonary embolism (PE) was confirmed by computed-tomography pulmonary angiogram or a high probability ventilation/perfusion lung scan. AF patients were those with non-valvular AF as defined by the European Heart Rhythm Association (EHRA) and was confirmed by electrocardiography.

This work was reviewed by the Research and Innovation department at Manchester University NHS Foundation Trust (MFT) who considered this a retrospective audit. Further review undertaken by MFTs clinical audit department led to registration onto the departmental audit portfolio. Standard HRA advice is consistent with this being categorised as a retrospective audit. All data is anonymised for publication.

Data collection

Electronic hospital records, clinic letters and hospital discharge summaries were used to collect information including details on hospital admissions, co-morbidities and information relating to DOAC use. Patients were limited to those whose base hospital was Manchester University NHS Foundation Trust to ensure access to hospital admission data.

For patients who had initiated a DOAC prior to January 2018 and continued to take it during the study period, their bleeding and thrombotic outcomes were examined from the time when they initiated the DOAC. Patients were followed until death, DOAC discontinuation or the end of the audit period, 1st October 2020.

Outcomes

The primary outcome was whether trough and peak DOAC levels were within the expected ranges documented in the International Council for Standardisation in Haematology (ICSH) recommendations or published literature[18, 19]. The secondary outcomes include new onset or recurrent VTE, new onset stroke during anticoagulant therapy, major bleeding as defined by the International Society of Thrombosis and Haemostasis (ISTH)[20] which includes: bleeding leading to a decrease in haemoglobin (Hgb)≥2 g/dl at any time point, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular, or retroperitoneal bleed) or clinically relevant non-major bleeding (CRNMB) which is any sign of bleeding that does not fit the ISTH definition of major bleeding but requires medical intervention, leads to hospitalisation or requires a face to face review[21].

Treatment regimes

Patients were either taking apixaban, rivaroxaban or edoxaban dosed as their Cockcroft-Gault creatinine clearance (C-G CrCl). Cockcroft-Gault creatinine clearance was also calculated using actual bodyweight unless the patient was >100kg where adjusted bodyweight was used. Adjusted bodyweight was calculated using the MDCalc adjusted bodyweight calculator requiring height, weight and sex. Appropriateness of dosing was determined by the manufacturers prescribing information for each DOAC. Once patients had a CrCl<15ml/min they were switched to warfarin due to the unlicensed nature of DOACs in this setting and potential for candidates to be placed on

transplant waiting list. The calcineurin inhibitors were dosed as per levels with individualised target trough levels.

Blood samples and assays

Renal function was lab reported using CKD-EPI. The renal function recorded was the result reported on the same date the DOAC levels were taken. Blood samples that were taken when the patient was experiencing an acute kidney injury were excluded. Acute Kidney Injury(AKI) was defined using serum creatinine values according to Kidney Disease Improving Global Outcomes (KDIGO)-criteria as follows [(22)]: stage 1—increase in serum creatinine by 26.5micromol/L within 48 hours or a 1.5 to 1.9 times increase in serum creatinine from baseline within 7 days; stage 2—2.9 times increase in serum creatinine within 7 days; stage 3—3 times or more increase in serum creatinine within seven days or initiation of renal replacement therapy. For comparison the Modified Diet in Renal Disease (MDRD) was calculated using the MDCalc MDRD calculator requiring serum creatinine, age, sex and race.

Trough tacrolimus, ciclosporin and sirolimus levels were recorded at the clinic visit before and after initiation of the DOAC. This would cover a 6-month period based upon a clinic frequency of three months. In patients who had started a DOAC within one month of transplant we could not obtain a suitable baseline trough CNI level.

Patients were taking a DOAC for at least 4 weeks prior to DOAC level sampling to ensure the patient was at steady-state. All patients taking DOACs prior to 2018 had DOAC levels taken in the study period, between January 2018 and October 2020. Patients were advised to avoid taking their usual dose of DOAC prior to sampling for trough levels and then after taking the dose had a further blood sample taken 2 hours after apixaban and edoxaban or 3 hours following rivaroxaban.

Blood samples used for DOAC analysis were anticoagulated with 3.2% citrated plasma. Analysis of the DOAC levels was carried out on the Sysmex CS5100 analyser using chromogenic analysis methodology. The BIOPHEN™ Heparin LRT kit is an anti-Xa chromogenic method for the in vitro

quantitative determination of heparin and theirs analogs. This method is appropriate for the Apixaban, Rivaroxaban and Edoxaban assay, direct Factor Xa (FXa) inhibitors. Quality control samples with known concentrations are run at two levels consistent with peak and troughs prior to analysis of any samples.

An EDTA blood sample was used for the measurement of Tacrolimus and ciclosporin quantitatively by LC-MS/MS using a TSQ Endura tandem quadrupole mass spectrometer (Thermo Fisher Scientific).

Statistical analysis

Categorical variables are presented as a number and percentage and continuous variables are presented throughout as median and interquartile range. DOAC levels are represented in box and whisker plots. The box representing the median, 25th and 75th centiles with the lines extending from the boxes indicating variability outside the quartiles. Any outliers are represented by a dot.

For tacrolimus and ciclosporin a change of <20% in levels before and after starting a DOAC was deemed to have low variability.

Results

Between January 2018 to October 2020 there were thirty-one renal transplant patients taking DOACs. The majority of patients were male, 74%. Eighteen patients had AF and fifteen had experienced at least one VTE event with two patients taking DOACs for both indications. Median time to DOAC initiation post-transplant was 7 years (range 0-24years) and the median follow up whilst taking a DOAC was 1year (range 3months-6.2 years). Thirteen patients were already taking DOACs prior to January 2018 for which they had been taking DOACs for a median duration of 14 months at the start of the study period. Ten of these patients were taking it for AF with the remainder taking it for VTE. Two patients with VTE had started the DOAC therapy within the two months prior to January 2018. At the end of the follow up period thirteen patients were still taking

DOAC therapy. Five patients had completed a DOAC course for VTE, six patients had switched from DOAC to warfarin due to CrCl<15ml/min, one patient discontinued DOAC due to a major bleed, and one patient switched to warfarin due to high DOAC levels. Five patients died before the end of the study period. Eight patients on DOACs had a CrCl<30ml/min. Demographics and clinical characteristics are summarised in Table 1.

Twenty-nine patients (94%) were taking a calcineurin inhibitor(CNI) of which twenty-four were taking tacrolimus and five patients taking ciclosporin. Twenty-five patients had CNI levels before and after DOAC was initiated. Prior levels were not available for three patients who initiated DOAC within one month post-transplant and one patient switching to tacrolimus when DOAC was initiated.

Twenty-six patients (84%) had DOAC levels recorded. Of the five patients without levels one patient took edoxaban in the evening so sampling could not be undertaken, two patients switched to warfarin due to a CrCl<15ml/min before level sampling and one patient expired. Those without DOAC levels were taking them for a much shorter period than those who did have levels 10.6 months versus 24.8 months respectively. One patient taking apixaban 2.5mg bd had an episode of acute kidney injury stage 3 when levels were taken so these were excluded.

DOAC dosing

In those taking a DOAC for VTE eight patients received loading doses, either apixaban 10mg bd for 7days or rivaroxaban 15mg bd for 21days. The remainder received >7 days low molecular weight heparin before initiating a DOAC or had been switched from warfarin in primary care by their general practitioner.

There were discrepancies between the number of patients with C-G CrCl 30-49ml/min and >50ml/min as compared to CKD-EPI and MDRD eGFR, table 1, but these discrepancies would only have led to one potential dosing error. The patient would have received 15mg of rivaroxaban with

the CKD-EPI and MDRD equations instead of the 20mg they were prescribed for AF. During the evaluation period three patients switched to warfarin due to deterioration in renal function below CrCl 15ml/min. Due to COVID-19 one patient was switched to a DOAC from their warfarin therapy. Only one patient was taking a DOAC that was not dosed as per manufacturers recommendations for renal function. The patient took 15mg rivaroxaban daily for AF with a CrCL>50ml/min and this was changed following clinic review. The low peak level was the outlier presented in figure 1.

One patient taking edoxaban 60mg in the evening was switched to apixaban 5mg bd due to renal function fluctuating around 50ml/min where edoxaban would require dose amendment.

There were two patients taking concomitant treatments that also had potential to interact with DOACs. These included a patient on verapamil a strong p-glycoprotein and CYP3A4 inhibitor and one patient on carbamazepine a potent CYP3A4 inducer.

Outcomes

Overall 94% (62/66) of DOAC levels were within the recommended ranges suggested by the ISCH and manufacturers information (figures 1 & 2). One patient on apixaban 5mg bd had high trough and peak levels and they were switched back to warfarin. The patient had reduced muscle mass due to immobility. One patient on edoxaban 30mg daily had high trough and peak levels, table 2. Five patients with CrCl< 30ml/min had ten DOAC levels all of which were in the therapeutic range. A sub-group analysis of patients with a CrCl <30ml/min is presented in Table 3.

There were no embolic events reported in patients taking DOACs, table 4. One patient went on to develop post-thrombotic syndrome following a DVT. There were two major bleeding episodes consisting of haematuria and haemoptysis both requiring admission to hospital with a Hgb drop >2g/dL. There were two episodes of clinically relevant non-major bleed presenting as haematuria

and rectal bleeding with a Hgb drop<2g/dL both requiring medical attention. Overall bleeding rates were 12.9% (4/31) with 6.5% patients experiencing a major bleed. Mean follow up for 31 patients on DOACs was 22.6 months (i.e. 58 patient-years at risk). The overall bleeding rate was 6.9 per 100 patient-years at risk.

The patient taking edoxaban 30mg daily had previously been prescribed apixaban 5mg bd for NVAF but only taking this once daily due to severe bruising. The patient permanently discontinued all anticoagulant therapy after a major bleed on edoxaban.

Five patients died whilst taking DOAC therapy although none of these deaths were related to thrombotic or bleeding events. Deaths were related to pneumonia, malignancy and severe heart failure.

Twenty-three patients (92%) had no significant variability in CNI level (<20% change) when DOAC was initiated. One patient had an intentional tacrolimus target trough level reduction to 3-5ng/L during the time when DOAC was started due to ongoing infection and recurrent cancer which is the outlier represented in supplementary figure 1. The remaining patient had variation in tacrolimus levels >20% but<30%. CNI levels are represented in supplementary figures 1 and 2.

Discussion

In this paper we describe a large UK transplant centres experience of using DOACs in 31 kidney transplant recipients with CrCl≥15ml/min. This is largest series examining DOAC levels to assess the safety of potential interactions in kidney transplant recipients and the only study to do this in patients with CrCl<30ml/min. We found no evidence of a significant interaction with apixaban, rivaroxaban and CNIs based on expected DOAC and CNI levels. Their use was found to be safe and effective with no VTE events and bleeding episodes at similar rates to published trial data with no bleeding related mortality.

The use of DOACs brings significant convenience for patients and clinicians in that routine level monitoring is not necessary, unlike with warfarin. However, in clinical practice there are suggestions that DOAC level monitoring may be warranted in certain populations. These populations include extremes of bodyweight, renal impairment and those taking drugs that impact on the CYP3A4 and P-glycoprotein pathways, such as the calcineurin inhibitors [9, 12, 18, 23, 24]. It would be useful to measure peak concentrations of DOACS (2–4 h after drug intake) to confirm there is adequate drug where absorption may be impaired or to ensure there is no excess drug circulating in the plasma. Determining trough DOAC concentrations would help to identify drug accumulation in renal impairment and determine the impact of drug interactions and extremes of bodyweight. The ICSH produced recommendations for laboratory monitoring of DOAC levels and within this document are references for peak and trough DOAC levels based on clinical studies [18].

To date there are few published studies reporting on the interaction with DOACs and calcineurin inhibitors, highlighted by the EHRA DOAC guidelines, and these studies are conflicting. The most recent paper to examine DOAC levels in thirteen kidney transplant recipients found that apixaban and rivaroxaban trough levels were as expected compared to published literature with the exception of two patients on rivaroxaban [23]. Both these patients had high levels. Another study by Camporese et al looked at eight kidney transplant recipients taking tacrolimus who were newly initiating rivaroxaban[25]. They concluded rivaroxaban was safe with no apparent interaction based on trough and peak levels over the first two weeks of treatment. This group had specific criteria for rivaroxaban initiation and excluded those with new VTE due to concerns over the large rivaroxaban loading doses; so patients were treated with LMWH and established on warfarin prior to starting rivaroxaban[25]. In 2014, Wannhoff et al examined trough rivaroxaban levels in nine liver transplant recipients and suggested that only ciclosporin interacted with rivaroxaban and not tacrolimus[26]. However patients on ciclosporin in this study had a significantly lower CrCl with a longer time since liver transplant which may have played a role in the increased DOAC levels. This study may have had

an impact on prescribing practices in the US with a recent survey of DOAC utilisation in solid organ transplants finding that out of 96 transplants centres 43.6% would avoid concomitant ciclosporin therapy and 13.5% would reduce the dose of DOAC with ciclosporin[27]. Among five patients in our evaluation taking ciclosporin therapy DOAC levels were within the expected ranges suggesting that it is not necessary to avoid the combination.

One publication details DOAC-CNI interaction in healthy volunteers and the effect of CNIs on overall DOAC exposure. Apixaban 10mg was given daily for three days with once daily tacrolimus or ciclosporin[28]. The findings suggested there was no effect on the overall apixaban AUC with CNIs although dosing regimens used in this paper are lower than that in clinical practice and healthy volunteers do not represent the complexity seen in a real-world population. Because of the lack of published studies, the EHRA 2021 guidelines recommend avoiding dabigatran with calcineurin inhibitors and suggest to consider avoiding the use of apixaban, edoxaban and rivaroxaban in patients on tacrolimus[12]. The EHRA suggest the possibility of referral for DOAC level monitoring in the case of more complex interactions. The findings from our centre would not support the need for a DOAC dose reduction with apixaban or rivaroxaban in patients on tacrolimus or ciclosporin. We also have eight patients with DOAC levels taken after receiving loading doses for VTE treatment with no deviation from expected level ranges which should negate some of the concern that was proposed by Camporese et al[25]. There were five patients in our study who did not undergo level monitoring. They had a much shorter follow up on DOAC therapy compared to those with levels taken making it difficult to be able to draw comparisons, although if they were removed from the overall analysis there was minimal impact upon overall outcomes.

There is a theoretical possibility of an interaction caused by DOACs which could increase CNI levels. All DOACs are substrates of P-Glycoprotein and rivaroxaban and apixaban have a degree of CYP3A4 metabolism[11]. So if the DOACs had an inhibitory effect upon either of these pathways, it may affect CNI levels requiring more frequent monitoring. A study by Vanhove and colleagues examined

factors that could affect CNI variability in transplant recipients initiating DOACs and found that DOAC had a <20% impact upon CNI levels which was unlikely to result in dose adjustments[29]. Similar findings were seen by Bukhari who found that 3 days after DAOC initiation there was no significant change in CNI level(30). Our findings are consistent with both of these studies with many of our patients having CNI variability <20%. A CNI variability >30% has been shown to be associated with de novo donor specific antibodies (DSA) and increased death-censored graft loss and would be of concern to clinicians [31, 32].

Although there were two patients taking other drugs perceived to interact with DOACs, verapamil and carbamazepine, apixaban levels remained within the expected ranges. It is worth noting the carbamazepine was for a peripheral neuropathy and so the dose was low, and carbamazepine has a dose dependant CYP3A4 induction(33). If DOACs are used with interacting drugs DOAC level monitoring should be considered[12].

The bleeding rates in our study are similar to what was seen in the major DOAC trials versus warfarin[34, 35] suggesting their use is safe in our renal transplant cohort, although there are limited events in our population. There have been a small number of recent comparative studies looking at thromboembolic and bleeding outcomes in kidney transplant recipients taking DOACs versus warfarin. Leon et al found a significant reduction in bleeding events with DOACs compared to warfarin in a total of 102 kidney transplant recipients[23]. There were no major bleeding events reported in either group. In a study by Bixby et al there was no significant difference between warfarin and DOACs in major bleeding or thromboembolic events in 197 kidney transplant recipients[36]. These studies are both underpowered to detect significant differences in events and are both small studies with no formal matching between the groups. A systematic review undertaken by Bixby et al found that DOACs had similar efficacy to warfarin with potentially lower

bleeding risks across a range of solid organ transplants[24]. The combined findings from these studies provide some reassuring data that DOACs are safe and effective in this population.

For kidney transplant recipients KDIGO guidelines recommend that any renal function estimating equation could be used to estimate transplant function[37] and both CKD-EPI and MDRD equations have been tested in this setting[38]. We routinely use CKD-EPI to estimate renal function however the randomised clinical trials for the DOACs used Cockcroft-Gault CrCl (C-G CrCl) so all patients were dosed based on C-G CrCl[14-17]. There are concerns that not using C-G CrCl could lead to dosing discrepancies and adverse outcomes such as bleeding and thrombotic events[39, 40]. In our small study the use of CKD-EPI or MDRD would have only led to one dosing discrepancy. Further large-scale studies are required to assess whether CKD-EPI or MDRD would be appropriate to use for dosing DOACs.

Five of the patients in this study with CrCl< 30ml/min had DOAC levels which were in the expected level range. Although these are small numbers these patients are being successfully and safely manged on DOAC therapy. Bixby et al is the only other study to date which included seven kidney transplant recipients taking DOACs with a CrCl<30ml/min[36]. The focus of their study was on clinical outcomes and did not include any DOAC level monitoring. In the multivariate cox regression analysis for major bleeding they did not find eGFR to be a significant factor although this may be related to small participant numbers. More advanced renal disease is known to be associated with an increased risk of bleeding including intracranial haemorrhage and gastrointestinal bleeding[41-44]. There is limited safety and efficacy data with DOACs in patients with a CrCl<30ml/min (<25ml/min with apixaban) due to the DOAC randomised controlled trials excluding this population[9]. This is despite edoxaban, apixaban and rivaroxaban being licensed down to a CrCl of 15ml/min. However, there are now increasing publications of DOAC use compared to warfarin for AF in the setting of dialysis or advanced CKD. This relates to the Food and Drug Administration licensing apixaban and rivaroxaban for dialysis patients based on small pharmacokinetic studies. Current observational

studies suggest DOACs are as effective with similar or preferable bleeding rates to warfarin(45-50). Benefits of anticoagulation for AF in the dialysis population is still uncertain, with Mavrakanas et al showing no reduction in stroke but increased bleeding rates when apixaban was compared to no anticoagulation[51]. An ongoing pilot RCT may shed more light on this[52]. It is worth noting that the European Medicines Agency have not licensed any DOAC below a CrCl of 15ml/min, although in practice they some European centres are using them at reduced doses for AF (53).

One patient with high trough and peak DOAC levels may be related to difficulties in estimating renal function. The patient was immobile and likely to have very low muscle mass. This patient was switched back to warfarin as there is no data that suggest adjusting DOAC dose should be undertaken based on levels[9] and this patient was high thrombotic risk due to recurrent VTE and AF. Level monitoring may well be indicated in situations where assessment of renal function proves difficult.

It is important to consider that kidney transplant recipients are at greater risk of AKI given their pre-existing CKD and pre-disposing co-morbidities. One patient that presented with a stage 3 AKI during the study period and had an extremely high apixaban trough level of 271ng/mL. It took 5 days during the patients admission for this level to drop below 30ng/mL. This highlights the importance of regular assessment of renal function as per EHRA guidance with DOAC dose review at regular intervals[12].

This study is limited to a single centre and due to small numbers, only a limited number of events occurred. There is the possibility of missing patients who presented to the General Practitioners as these records were not accessed and would have required individual patient consent. The strengths of this study are the inclusion of patients with severe renal function, CrCl<30ml/min, utilisation of DOAC level monitoring and the long period of follow up.

We are unable to draw any conclusions on the use of dabigatran and edoxaban in a renal transplant population. We had no patients taking dabigatran which was likely due to its high renal excretion (80%) and being contraindicated with CrCL <30ml/min. Our experience with edoxaban was also limited to one patient that had high levels which precludes us from making any recommendations with this agent.

Conclusion

The use of apixaban and rivaroxaban in kidney transplant recipients appears to be safe. There is no evidence of a significant interaction with ciclosporin or tacrolimus as evidenced by DOAC levels and CNI levels. There were no safety concerns regarding thromboembolic and bleeding events with bleeding rates similar to those seen in the major DOAC randomised controlled trials. The findings from this evaluation are reassuring but larger studies are warranted to demonstrate the safety of DOACs in a kidney transplant population.

Data availability

The data that support the findings of this study are available from the corresponding author, KP, upon reasonable request.

Disclosures

KP is supported by the National Institute for Health Research (HEE/ NIHR ICA Programme Clinical Doctoral Research Fellowship, NIHR300545). SM is supported by NIHR Infrastructure in Manchester and Devices for Dignity MIC, Sheffield. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

Acknowledgements

Lynne Keighley Chief Biomedical Scientist for Coagulation

Dr Tim Morris Consultant Chemical Pathologist

Sister Lisa Laycock and the kidney transplant clinic team

Author contributions

KP, JT, MM, MP, SB were involved in the concept and design. KP, JC were involved in data collection. KP drafted the article. All authors were involved in critically revising the paper. All authors approve the final version for publication.

References

1. Verhave JC, Tagalakis V, Suissa S, Madore F, Hebert MJ, Cardinal H. The risk of thromboembolic events in kidney transplant patients. Kidney Int. 2014;85(6):1454-60.
2. Poli D, Zanazzi M, Antonucci E, Bertoni E, Salvadori M, Abbate R, et al. Renal transplant recipients are at high risk for both symptomatic and asymptomatic deep vein thrombosis. Journal of Thrombosis and Haemostasis2006. p. 988-92.
3. Lentine KL, Schnitzler MA, Abbott KC, Li L, Xiao H, Burroughs TE, et al. Incidence, predictors, and associated outcomes of atrial fibrillation after kidney transplantation. Clin J Am Soc Nephrol. 2006;1(2):288-96.
4. Abbott KC, Reynolds JC, Taylor AJ, Agodoa LY. Hospitalized atrial fibrillation after renal transplantation in the United States. Am J Transplant. 2003;3(4):471-6.
5. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378(9800):1419-27.
6. Malyszko J, Lopatowska P, Mlodawska E, Musialowska D, Malyszko JS, Tomaszuk-Kazberuk A. Atrial fibrillation in kidney transplant recipients: is there a place for the novel drugs? Nephrol Dial Transplant. 2018;33(8):1304-9.
7. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database Syst Rev. 2017;11(11):CD011373-CD.
8. Wolfe Z, Khan SU, Nasir F, Raghu Subramanian C, Lash B. A systematic review and Bayesian network meta-analysis of risk of intracranial hemorrhage with direct oral anticoagulants. J Thromb Haemost. 2018;16(7):1296-306.
9. Parker K, Thachil J. The use of direct oral anticoagulants in chronic kidney disease. British Journal of Haematology. 2018;183(2):170-84.

10. Chan N, Sobieraj-Teague M, Eikelboom JW. Direct oral anticoagulants: evidence and unresolved issues. The Lancet. 2020;396(10264):1767-76.
11. Zhang Y, Souverein PC, Gardarsdottir H, van den Ham HA, Maitland-van der Zee AH, de Boer A. Risk of major bleeding among users of direct oral anticoagulants combined with interacting drugs: A population-based nested case-control study. Br J Clin Pharmacol. 2020;86(6):1150-64.
12. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. EP Europace. 2021.
13. Douxfils J, Ageno W, Samama C-M, Lessire S, ten Cate H, Verhamme P, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. Journal of Thrombosis and Haemostasis. 2018;16(2):209-19.
14. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. New England Journal of Medicine. 2011;365(10):883-91.
15. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2013;369(22):2093-104.
16. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2011;365(11):981-92.
17. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. New England Journal of Medicine. 2009;361(12):1139-51.
18. Douxfils J, Adcock DM, Bates SM, Favaloro EJ, Gouin-Thibault I, Guillermo C, et al. 2021 Update of the International Council for Standardization in Haematology Recommendations for Laboratory Measurement of Direct Oral Anticoagulants. Thromb Haemost. 2021;121(8):1008-20.
19. Eliquis product information 2011 [cited 2021 03/02/2021]. Available from: https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf.
20. SCHULMAN S, KEARON C, SCIENTIFIC tSOCOAOT, THROMBOSIS SCOTISO, HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis. 2005;3(4):692-4.
21. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Anticoagulation tSoCo. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis. 2015;13(11):2119-26.
22. KDIGO. Acute Kidney Injury. Kidney International. 2012;2.
23. Leon J, Sabbah, L. , Aubert, O. , Anglicheau, D. , Delavenne, X. , Zuber, J. , Amrouche, L. , Scemla, A. , Giura, G. , Divard, G. , Legendre, C. & Sberro-Soussan, R. . Efficacy and Safety of Direct Oral Anticoagulants in Kidney Transplantation. . Transplantation. 2020;104(12):2625-31.
24. Bixby AL, Lichvar AB, Salerno D, Park JM. Use of direct-acting oral anticoagulants in solid organ transplantation: A systematic review. Pharmacotherapy. 2020.
25. Camporese G, Bernardi D, Bernardi E, Avruscio GP, Marchini F, Bonfante L, et al. Absence of interaction between rivaroxaban, tacrolimus and everolimus in renal transplant recipients with deep vein thrombosis or atrial fibrillation. Vascul Pharmacol. 2020;130:106682.
26. Wannhoff A, Weiss KH, Schemmer P, Stremmel W, Gotthardt DN. Increased levels of rivaroxaban in patients after liver transplantation treated with cyclosporine A. Transplantation. 2014;98(2):e12-3.
27. Lichvar AB, Pierce DR, Salerno D, Klem P, Waldman G, Park JM. Utilization of direct-acting oral anticoagulation in solid organ transplant patients: A national survey of institutional practices. Clinical Transplantation. 2020;34(6):e13853.

28. Bashir B, Stickle DF, Chervoneva I, Kraft WK. Drug-Drug Interaction Study of Apixaban with Cyclosporine and Tacrolimus in Healthy Volunteers. Clinical and translational science2018. p. 590-6.
29. Vanhove T, Spriet I, Annaert P, Maertens J, Van Cleemput J, Vos R, et al. Effect of the Direct Oral Anticoagulants Rivaroxaban and Apixaban on the Disposition of Calcineurin Inhibitors in Transplant Recipients. Ther Drug Monit. 2017;39(1):77-82.
30. Bukhari MA, Al-Theaby A, Tawhari M, Al-Shaggag A, Pyrke R, Gangji A, et al. Efficacy and safety of non-vitamin K antagonist oral anticoagulants post-kidney transplantation. World J Transplant. 2019;9(6):134-44.
31. O'Regan JA, Canney M, Connaughton DM, O'Kelly P, Williams Y, Collier G, et al. Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation. J Nephrol. 2016;29(2):269-76.
32. Rodrigo E, Segundo DS, Fernández-Fresnedo G, López-Hoyos M, Benito A, Ruiz JC, et al. Within-Patient Variability in Tacrolimus Blood Levels Predicts Kidney Graft Loss and Donor-Specific Antibody Development. Transplantation. 2016;100(11):2479-85.
33. Perucca E, Hedges A, Makki KA, Ruprah M, Wilson JF, Richens A. A comparative study of the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. Br J Clin Pharmacol. 1984;18(3):401-10.
34. Hylek EM, Held C, Alexander JH, Lopes RD, Caterina RD, Wojdyla DM, et al. Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin. Journal of the American College of Cardiology. 2014;63(20):2141-7.
35. Goodman SG, Wojdyla DM, Piccini JP, White HD, Paolini JF, Nessel CC, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). Journal of the American College of Cardiology. 2014;63(9):891-900.
36. Bixby AL, Shaikh SA, Naik AS, Cotiguala L, McMurry K, Samaniego-Picota MD, et al. Safety and efficacy of direct-acting oral anticoagulants versus warfarin in kidney transplant recipients: a retrospective single-center cohort study. Transpl Int. 2020;33(7):740-51.
37. KDIGO. KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients. American Journal of Transplantation. 2009;9:si-si.
38. Shaffi K, Uhlig K, Perrone RD, Ruthazer R, Rule A, Lieske JC, et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2014;63(6):1007-18.
39. Kruger PC, Robinson MA, Xu K, Siegal DM, Eikelboom JW, Bhagirath VC. Assessing renal function in patients receiving DOACs: Cockcroft-Gault versus estimated glomerular filtration rate. Thromb Res. 2017;157:165-6.
40. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, et al. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. Journal of the American College of Cardiology. 2017;70(21):2621-32.
41. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nature Reviews Nephrology. 2018;14(5):337-51.
42. Bos MJ, Koudstaal PJ, Hofman A, Breteler MMB. Decreased Glomerular Filtration Rate Is a Risk Factor for Hemorrhagic But Not for Ischemic Stroke. Stroke. 2007;38(12):3127-32.
43. Iseki K, Kinjo K, Kimura Y, Osawa A, Fukiyama K. Evidence for high risk of cerebral hemorrhage in chronic dialysis patients. Kidney Int. 1993;44(5):1086-90.
44. Sood P, Kumar G, Nanchal R, Sakhuja A, Ahmad S, Ali M, et al. Chronic kidney disease and end-stage renal disease predict higher risk of mortality in patients with primary upper gastrointestinal bleeding. Am J Nephrol. 2012;35(3):216-24.
45. J.W. S, S.D. P, G.M. C, S.H. H, D.M. W, S. G, et al. Apixaban Versus Warfarin in Patients with Atrial Fibrillation and Advanced Chronic Kidney Disease. Circulation. J.W. Stanifer, Munson

Nephrology, Munson Healthcare, 4062 W Royal Drive, Traverse City, MI 49694, United States. E-mail: jstanifer@mhc.net: Lippincott Williams and Wilkins (E-mail: kathiest.clai@apta.org); 2020. p. 1384-92.
46. Reed D, Palkimas S, Hockman R, Abraham S, Le T, Maitland H. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Research and Practice in Thrombosis and Haemostasis. 2018;2(2):291-8.
47. Schafer JH, Casey AL, Dupre KA, Staubes BA. Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease. The Annals of pharmacotherapy. 2018;52(11):1078-84.
48. Stanton BE, Barasch NS, Tellor KB. Comparison of the Safety and Effectiveness of Apixaban versus Warfarin in Patients with Severe Renal Impairment. Pharmacotherapy. 2017;37(4):412-9.
49. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Hemodialysis. J Am Coll Cardiol. 2020;75(3):273-85.
50. Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrol Dial Transplant. 2019;34(2):265-77.
51. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146-54.
52. Harel ZW, R. Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis (SAFE-D). 2019.
53. Potpara TS, Ferro C, Lip GYH, Dan GA, Lenarczyk R, Mallamaci F, et al. Management of atrial fibrillation in patients with chronic kidney disease in clinical practice: a joint European Heart Rhythm Association (EHRA) and European Renal Association/European Dialysis and Transplantation Association (ERA/EDTA) physician-based survey. EP Europace. 2020;22(3):496-505.

N	31
Age (median, IQR)	66 (53-74)
Male sex, n (%)	23 (74%)
Time since transplant, years Median (IQR)	10 (5-18)
Reason for transplant:	
Hypertension, n	2

Diabetes, n	4
Polycystic kidney disease, n	5
IgA nephropathy, n	3
Other/unknown, n	7
CrCl ml/min, n	
≥50	14
30-49	9
<30	8
CKD-EPI ml/min/1.73m^2, n	
≥50	10
30-49	13
<30	8
MDRD ml/min/1.73m^2,n	
≥50	13
30-49	10
<30	8
Indication for Anticoagulant:	
VTE (DVT/PE), n	15 (4/11)
NVAF, n	18
Time on DOAC in months, Median (IQR)	12 (3-39)
Immunosuppresion regime:	
CNI+MMF/AZA, n	14
CNI+MMF/AZA+Prednisolone, n	7
CNI only, n	5
Other	5
Concomitant antiplatelet	3

CHA_2DS_2-VASc, mean +SD	3.6 ±1.3
HASBLED mean+SD	1.6±0.8
Albumin g/dL, Median (IQR)	35 (32-38)

Table 1. Demographics of patients with kidney transplant

Interquartile range (IQR 25th-75th centile), Cockcroft-Gault Creatinine Clearance (CrCl), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modified Diet in Renal Disease (MDRD), Venous Thromboembolism (VTE), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Non-Valvular Atrial Fibrillation (NVAF), Direct Oral Anticoagulant (DOAC), Calcineurin Inhibitor (CNI), Mycophenolate Mofetil(MMF), Azathioprine (AZA), Standard Deviation (SD), CHA_2DS_2-VASc (Congestive Cardiac Failure, Hypertension, Age>75 2 points, Diabetes, Stroke 2 points, Vascular disease, Age 64-75 1 point, Sex female), HASBLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding tendency, Labile INR, Age>65).

DOAC regime	Number of patients	Number trough levels	Number peak levels	C_{trough} range,ng/mL (25th-75th centile)	ICSH trough reference ranges ng/ml, median (5th-95th centile)	C_{peak} range, ng/mL (25th-75th centile)
Apixaban 2.5mg bd	5	5	3	73-135 (85-131)	NVAF 79 (34-162) VTE 32 (11-90)	131-201 (132-167)
Apixaban 5mg bd	20	26	20	36-215 (72-112)	NVAF 103 (41-230) VTE 63 (22-177)	94-371 (135-262)
Rivaroxaban 20mg od	2	2	2	11-75 (27-59)	NVAF 44 (12-137) VTE 32 (6-239)	408-417 (410-415)
Rivaroxaban 15mg od	3	4	4	16-54 (26-40)	As 20mg	182-548 (351-447)
Edoxaban 30mg od	1	1	1	117	NVAF 27 (15-45) VTE 16 (8-32)	119
Edoxaban 60mg od*	1	0	0	n/a	NVAF 36 (19-62) VTE 19 (10-39)	n/a

Table 2. DOAC regimes and levels.

Direct Oral Anticoagulant (DOAC), Once daily (od), Twice daily (bd), Trough concencentration (C_{trough}), Peak concentration (C_{peak}), International Council for Standardisation in Haematology (ICSH), Non-valvular atrial fibrillation (NVAF). Venous thromboembolism (VTE)

* One patient switched from Edoxaban 60mg daily to Apixaban 5mg twice daily so this patient has been recorded separately under each DOAC.

N	8				
Age, median IQR	74 (51-78)				
Time since transplant, years median (IQR)	15.5 (11.5-17)				
Indication, AF/VTE/Both	5/ 2 /1				
Time on DOAC, months median (IQR)	32 (15-44)				
IS Regime: CNI only MMF+Pred CNI+AZA/MMF	 4 1 3				
CNI levels, mean Ciclosporin Tacrolimus	 129 6				
CHA_2DS_2-VASc, mean +SD	3.8±1.3				
HASBLED mean+SD	1.8±0.9				
Albumin g/dL, Median (IQR)	34 (32-36)				
Anticoagulant regimes					
	N	C_{trough} range,	C_{peak} range, ng/ml	Thrombotic	Bleeding

		ng/ml ICSH median (5-95th centile)	 ICSH median (5-95th centile)	outcomes	outcomes
Apixaban 2.5mg bd	4	115-135 ICSH 79 (34-162)	133-218 ICSH 123 (69-221)	0	1 CRNMB
Apixaban 5mg bd	2	ND*	ND*	0	0
Rivaroxaban 15mg daily	2	35 ICSH 32 (6-239)	413 ICSH 215 (22-535)	0	0

Table 3. Sub-analysis of kidney transplant recipients with CrCl<30ml/min at time of analysis

IQR 25th-75th centile, Atrial Fibrillation (AF), Venous thromboembolism (VTE), Immunosuppression (IS), Calcineurin Inhibitor (CNI), Mycophenolate Mofetil (MMF), Azathioprine (AZA), CHA2DS2-VASc (Congestive Cardiac Failure, Hypertension, Age>75 2 points, Diabetes, Stroke 2 points, Vascular disease, Age 64-75 1 point, Sex female), HASBLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding tendency, Labile INR, Age>65), Trough concentration (Ctrough), Peak concentration (Cpeak), Clinically relevant non major bleed (CRNMB), International Council for Standardisation in Haematology (ICSH) range

*Not Done (ND) One patient with AF was switched to warfarin due to renal decline before levels could be taken (patient on incorrect dose) and another patient completed 3months of treatment for a VTE before levels could be done.

DOAC regime	Number of patients	Indication VTE/AF	Thrombotic events	Bleeding episodes	Time to bleeding event
Apixaban 2.5mg bd	5	1/4	0	1 Major 1CRNMB	37 months 49 months
Apixaban 5mg bd*	20	9/12	0	0	
Rivaroxaban	2	2/0	0	1 CRNMB	18 months

20mg od					
Rivaroxaban 15mg od	3	2/2	0	0	
Edoxaban 30mg od	1	0/1	0	1 Major	1 month
Edoxaban 60mg od*	1	0/1	0	0	

Table 4. DOAC regimes and outcomes. Direct Oral Anticoagulant (DOAC), Venous Thromboembolism (VTE), Atrial Fibrillation (AF), Clinically Relevant Non-Major Bleed (CRNMB), Once daily (od), Twice daily (bd)

* One patient switched from Edoxaban 60mg daily to Apixaban 5mg twice daily so this patient has been recorded separately under each DOAC.