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Direct oral anticoagulant considerations in solid organ transplantation: A review

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Abstract

For more than 60 years, warfarin was the only oral anticoagulation agent available for use in the United States. In many recent clinical trials, several direct oral anticoagulants (DOACs) demonstrated similar efficacy with an equal or superior safety profile, with some other notable benefits. The DOACs have lower inter- and inpatient variability, much shorter half-lives, and less known drug-drug and drug-food interactions as compared to warfarin. Despite these demonstrated benefits, the use of DOACs has not gained uniform acceptance because of lack of supportive data in special patient populations, including recipients of solid organ transplants maintained on immunosuppression. This review describes the properties of several novel DOACs including their pharmacology and mechanisms of action as they relate to use among solid organ transplant recipients. We have particularly focused on (i) dosing in patients with impaired renal and hepatic function; (ii) considerations for drug-drug interactions with immunosuppressive medications; and (iii) management of the anticoagulated patients at the time of unplanned surgery. The risks and benefits of the use of DOACs in solid organ transplant recipients should be carefully evaluated prior to the introduction of these agents in this highly distinct patient population.

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AUTHORS' CONTRIBUTIONS

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CONFLICT OF INTEREST

None.

Keywords

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1 INTRODUCTION

For more than 60 years, warfarin was the only standard oral anticoagulation agent available for use in the United States. As is well known, the use of warfarin requires close monitoring to ensure efficacy and safety, as well as avoidance of several drug-drug and drug-food interactions. The frequency and timing of such evaluations frequently result in difficulties and challenges in maintaining a stable therapeutic international normalized ratio (INR), with population estimates of the mean time within the therapeutic range between only 30% and 59%.¹ No alternative oral anticoagulant was available in the United States until the Food and Drug Administration (FDA)-approved dabigatran in 2010, as a potential alternative to warfarin for a variety of indications (Table 1). After the approval of dabigatran, three other oral agents were approved by the FDA: rivaroxaban in 2011, apixaban in late 2012, and edoxaban in early 2015.

The direct oral anticoagulants (DOACs) have a low inter- and inpatient variability which enables the use of standardized dosing recommendations and a wide therapeutic range, permitting their use without routine drug monitoring.² Currently available DOACs have a fast onset of action, with no requirement to bridge patients upon initiation for the prevention of nonvalvular atrial fibrillation (NVAf). The shorter half-life of DOACs of approximately 8–18 hours depends on the agent and health status of the recipient, and therefore, their quick offset of therapeutic effects allows for greater ease in planning elective surgeries based on estimated half-lives in specialized patient populations (Tables 2 and 3).^{3,4} Additionally, the new oral anticoagulants have few known drug-drug and drug-food interactions as compared to warfarin.⁵

While the acquisition cost of branded agents may initially be greater, a study utilizing a Markov model to assess the incremental cost-effectiveness and quality-adjusted life years of patients with nonvalvular atrial fibrillation found that edoxaban appears to be economically beneficial when compared with dose-adjusted warfarin.² Analyses for each of the DOACs found similar results.⁶ Despite these proposed clinical and economic benefits, there are insufficient data regarding the use of DOACs in selected patient populations. Dosing and treatment considerations of these agents have been reviewed previously.^{7–9} The purpose of this article was to describe the novel pharmacology and mechanisms of action of the new oral anticoagulants as they relate to their use among solid organ transplant recipients. This will include discussion of dosing in patients with impaired renal and hepatic function, considerations for drug-drug interactions with immunosuppressive medications, and management of patients at the time of unplanned surgery.

2 NOVEL MECHANISMS AND PHARMACOKINETICS

Dabigatran is a synthetic inhibitor of thrombin (Factor IIa). Due to limited bioavailability, dabigatran is formulated as a prodrug, dabigatran etexilate, which is a substrate of the P-glycoprotein (P-gp) efflux transporter. Considered a double prodrug, dabigatran etexilate is first hydrolyzed by carboxyl esterases to two mono prodrugs and then subsequently hydrolyzed to its active form in human plasma. Upon hydrolysis in the liver and in plasma, the active component reversibly binds to the catalytic domain of the thrombin enzyme (Figure 1). Dabigatran therefore inhibits fibrin-bound thrombin, free circulating thrombin, and thrombin-induced platelet aggregation.¹⁰ Further information regarding specific pharmacokinetics is summarized in Table 2.

Rivaroxaban, apixaban, and edoxaban are direct factor Xa inhibitors, but unlike heparin, they do not require antithrombin III cofactor to selectively block factor Xa. These agents can inhibit free and clot-bound factor Xa and prothrombinase activity. Rivaroxaban is metabolized via oxidative degradation catalyzed by cytochrome P450 3A4/5 and 2J2 enzymes and by hydrolysis. It is also a substrate for the P-glycoprotein efflux transporter. Apixaban is also metabolized via the cytochrome P450 isoenzymes, primarily 3A4 and 1A2, 2C8, 2C9, and 2J2. Edoxaban, on the other hand, is not highly bound to plasma proteins and undergoes minimal metabolism via hydrolysis, conjugation, or oxidation by CYP 450 enzymes.¹¹

3 RENAL IMPAIRMENT

Each of the DOACs undergoes some component of renal elimination (Table 2). In regard to exposure, it is therefore important to consider the effect of both acute and chronic renal impairment on each drug's area under the plasma concentration-time curve (AUC) and thereby its half-life which may vary. There is added complexity in the use of DOACs in the post-transplant setting, as the majority of patients will experience acute fluctuations in renal function (delayed graft function [DGF], acute illness, infection, rejection), be exposed to acute and chronic nephrotoxic agents (calcineurin inhibitors [CNIs], antibiotics), and utilize concomitant agents with known or unknown drug interactions, especially in relation to metabolism through the CYP450 enzyme pathway and P-gp transporter. Renal function must therefore be closely monitored when prescribing DOACs to transplant recipients and should only be used in patients with sufficient and stable renal function. Below, we briefly provide and summarize available data from a literature review regarding the use of DOACs in patients with renal and hepatic impairment in recipients of solid organ transplants.

3.1 Dabigatran in renal impairment

Approximately 80% of dabigatran is excreted as unchanged in the urine, and overall drug exposure is thought to increase with age and worsening of renal function.^{12,13} While the Randomized Evaluation of Long-Term Anticoagulation (RE-LY) study excluded patients with an estimated creatinine clearance (CL_{CR}) <30 mL/min, dabigatran has approved dosing for the reduction of stroke and systemic embolism in NVAF in patients with a CL_{CR} of 15–30 mL/min.^{14,15} This recommendation is largely based on two studies assessing the exposure of dabigatran in patients with renal impairment. In an open-label study which

investigated the effect of mild-to-severe renal impairment on drug exposure after a single 150 mg dose, the terminal elimination half-life of dabigatran increased from 13.8 hours in healthy subjects with normal renal function, to 16.6 hours, 18.7 hours, and 27.5 hours in patients with mild ($CL_{CR} >50$ to 80 mL/min), moderate ($CL_{CR} >30$ to 50 mL/min), and severe renal impairment ($CL_{CR} \leq 30$ mL/min), respectively.¹² This translates to 1.5-, 3.2-, and 6.3-fold higher AUC values in subjects with mild, moderate, and severe renal impairment, respectively. In another study, dabigatran plasma concentrations obtained during the RE-LY trial were analyzed in a pharmacokinetic simulation model, and the relationship between CL_{CR} and dabigatran exposure was found to be nonlinear.¹⁶ Various regimens including 75 mg twice daily, 110 mg daily, and 150 mg daily in patients with a CL_{CR} between 15 and 30 mL/min were expected to have similar drug exposure to that found among healthy subjects. Without any clinical data, the dose of 75 mg twice daily was chosen based on a lower peak-trough ratio than any single daily regimen and similar posology for all patient subgroups which might reduce medication errors and avoid a negative impact on adherence.^{16,17}

There has been recent concern in utilizing dabigatran even in patients with moderately decreased renal function (eGFR 50–80 mL/min/1.73 m²). A recent retrospective study utilizing the VA National Patient Care inpatient and outpatient claims and VA Decision Support System National Pharmacy and Laboratory extracts found that even in those patients who converted from warfarin to dabigatran with moderate renal dysfunction had a bleeding risk nearly three times higher when compared to patients who remained on warfarin.¹⁸ These data from real-world clinical use highlight significant concern for use of dabigatran in renal impairment.

3.2 Rivaroxaban in renal impairment

Despite relatively little dependence on renal excretion, each of the landmark trials which tested rivaroxaban including “Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation” (ROCKET-AF), “Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism” (EINSTEIN-PE investigators), and “Oral Rivaroxaban for Symptomatic Venous Thromboembolism” (EINSTEIN-DVT investigators) excluded patients with an estimated $CL_{CR} <30$ mL/min.^{19–21} However, the US prescribing information for rivaroxaban delineates dosing recommendations in patients with CL_{CR} 15–50 mL/min and NVAf, but not in patients with venous thromboembolism (VTE).²² A separate study in healthy volunteers investigated the pharmacokinetics of a single oral dose of 10 mg under fasting conditions, and the results were compared to those obtained in patients with various degrees of renal impairment. It was found that the area under the plasma concentration-time curve increased 1.44-fold, 1.52-fold, and 1.64-fold for patients with mild (CL_{CR} 50–79 mL/min), moderate (CL_{CR} 30–49 mL/min), and severe ($CL_{CR} \leq 30$ mL/min) renal impairment, respectively.²³ Another study which evaluated the pharmacokinetics of rivaroxaban after a single dose of 15 mg administered before and after hemodialysis in subjects with end-stage renal disease (ESRD) and in control subjects found that the patients on hemodialysis experienced a 56% increase in AUC and 35% decrease in overall drug clearance, similar to that described in patients with moderate or severe renal insufficiency.²⁴ Rivaroxaban has not

been studied for any indication in patients with renal impairment, and while the aforementioned increases in AUC values are modest, the risk of active drug accumulation which may result in bleeding cannot be extrapolated from these small pharmacokinetic studies and therefore for the present time should be avoided.

An analysis of prescriptions for DOACs in patients with ESRD on hemodialysis found increasing use of dabigatran and rivaroxaban. Based on prescription data from 2010 to 2014, the use of DOACs in this patient population resulted in a higher risk of hospitalization or death from bleeding for dabigatran (rate ratio, 1.48; 95% CI, 1.21–1.81; $P=.001$) and rivaroxaban (rate ratio, 1.38; 95% CI, 1.03–1.83; $P=.04$) when compared to warfarin.²⁵ This study demonstrates a growing trend toward the use of DOACs in patients excluded from clinical trials and emphasized the increased rate of complications that may ensue.

3.3 Apixaban in renal impairment

Only 27% of the dose of apixaban is excreted renally. In the “Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation” (ARISTOTLE) study, patients with NVAF were excluded if they had a serum creatinine >2.5 mg/dL or $CL_{CR} <25$ mL/min. Dose adjustments were made for patients meeting two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or a serum creatinine ≥ 1.5 mg/dL.²⁶ Other landmark studies for apixaban excluded patients with $CL_{CR} <25$ mL/min or impaired renal function.^{27–30} There are no other clinical trials which evaluated apixaban in patients with severe renal impairment. A prespecified secondary analysis of ARISTOTLE found that the renal impairment group, defined as $CL_{CR} <50$ mL/min, had higher rates of the primary outcome, all-cause mortality, and of major bleeding. Apixaban was more effective than warfarin in preventing stroke or systemic embolism, therefore resulting in reduced mortality irrespective of renal function, and was associated with fewer major bleeding events across all ranges of estimated glomerular filtration rate (eGFR).³¹ When analyzed in a meta-analysis of all six phase III studies, apixaban was associated with lower bleeding risk in patients with mild (CL_{CR} 50–80 mL/min) and similar risk in patients with moderate-to-severe ($CL_{CR} <50$ mL/min) renal insufficiency when compared to conventional agents.³² This is in parallel with two open-label studies which evaluated the effects of a single 10 mg dose of apixaban in otherwise healthy subjects which suggested that dose adjustments of apixaban on the basis of renal function alone are not warranted, because there are only moderate increases in AUC by 44% and 36% in patients with severe renal impairment and on hemodialysis, respectively.^{33,34}

3.4 Edoxaban in renal impairment

About 50% of edoxaban is recoverable as unchanged drug in the urine. Edoxaban is the only DOAC that is contraindicated in patients with NVAF despite normal renal function ($CL_{CR} >95$ mL/min) owing to lower edoxaban concentrations and a significantly increased risk of stroke or systemic embolism as compared to warfarin in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) study.^{35,36} The ENGAGE AF-TIMI 48 study excluded patients with $CL_{CR} <30$ mL/min and recommended a dose adjustment for patients with a CL_{CR} between 30 and 50 mL/min. Despite these findings, the US prescribing information provides

recommendations for the use of edoxaban for patients with CL_{CR} as low as 15 mL/min for NVAf based on an unpublished phase I study.³⁵ This is in opposition to an open-label single-dose study in which healthy patients with various classifications of renal insufficiency were given 15 mg of edoxaban and experienced increases in AUC by 32%, 74%, 72%, and 93% for patients with mild impairment (CL_{CR} 50–80 mL/min), moderate impairment (CL_{CR} 30–49 mL/min), severe impairment (CL_{CR} 30 mL/min), and those on peritoneal dialysis, respectively.³⁷ Little data are available regarding edoxaban use in patients on hemodialysis. An open-label study which evaluated the effect of a single dose of edoxaban in patients on hemodialysis found that total exposure of edoxaban was similar to that found in healthy patients with normal renal function. Notably, exposure for the pharmacologically active M-4 metabolite was much higher in this study as compared to previous studies.³⁸

Normal renal function did not have the same effect for patients being treated for VTE in the Hokusai-VTE study, and therefore, this contraindication has not been found to be applicable for the use of edoxaban for the VTE indication.³⁹ A pharmacokinetic analysis in a pooled population, with data obtained from 13 separate phase I studies and from the Hokusai-VTE trial, found that edoxaban dose adjusted to renal function resulted in reduced exposure compared with the standard-dose group; this dose reduction, however, did not lead to any clinical differences in the subgroup analyses.^{39,40} The prescribing information for edoxaban may be misleading because it recommends the use of the Cockcroft-Gault equation for estimating CL_{CR} . This may be problematic in solid organ transplant recipients as this may be an inaccurate representation of clearance in the setting of fluctuating renal function.³⁵

3.5 Recommendations for renal impairment

The ideal oral anticoagulant for use in patients with impaired renal function continues to be unknown; the choice of either warfarin or of a DOAC with less dependence on renal clearance may both be beneficial in this patient population. Regardless of the choice in oral anticoagulant, close monitoring still remains necessary in patients with poor or varying renal function as this has not been adequately studied in a controlled setting. Additional fluctuations in weight and doses of concomitant agents make the use of DOACs in this highly distinct patient population difficult to recommend. Based on low-quality evidence which include single-dose studies, apixaban appears to be the preferred agent in patients with renal insufficiency, but further studies are warranted.

4 HEPATIC IMPAIRMENT

Liver dysfunction plays an important role in the pharmacokinetics and pharmacodynamics effects of a drug. Patients with significant liver disease were excluded from phase III registration trials for the DOACs. Currently, none of the DOACs are contraindicated in hepatic impairment, although there are recommendations to avoid certain agents depending on the severity of the patient's liver dysfunction.^{15,22,35,41}

It is well known that drug absorption can be significantly affected in hepatic impairment; this is specifically found with compounds that undergo pivotal metabolic changes during the first-pass effect. Porto-systemic shunting can reduce the effect of drug-metabolizing enzymes by bypassing this presystemic processing, particularly in cirrhotic patients. None of

the DOACs have a high hepatic extraction ratio; therefore, differences in absorption in patients with hepatic impairment are generally not of major concern. It is important to note, however, that one of the DOACs, dabigatran, is a prodrug and thus may be subject to a reduction in the active form.⁹ In a single-dose study, 150 mg of dabigatran was administered to both healthy controls and to patients with chronic Child-Pugh class B liver disease. Conversion of the dabigatran intermediate to active dabigatran was slower in patients with hepatic impairment, but there were no differences in total drug exposure.⁴² The authors postulate that a porto-systemic shunting effect may have been responsible for the slower conversion, although the clinical effect of this delay is unknown. In transplant patients with known hepatic congestion prior to transplantation, porto-systemic shunting should be considered when using dabigatran.

Drug distribution in patients with hepatic impairment is likely to be altered due to a reduction in plasma proteins. An enhanced pharmacodynamic response may be seen with drugs that have high affinity for plasma proteins. Dabigatran and edoxaban are not highly protein bound and so their distribution should not be greatly affected by changes in plasma proteins. Rivaroxaban and apixaban, on the other hand, are 92%–95% and 87% protein bound in plasma, respectively.⁹ In a study involving otherwise healthy volunteers who received a single dose of 10 mg of rivaroxaban, patients with Child-Pugh class B hepatic impairment had a lower serum albumin at baseline, and this correlated with presence of a higher fraction of unbound rivaroxaban in the serum. This resulted in a prolonged prothrombin time (PT) in the group with hepatic impairment.⁴³

Liver disease is most often associated with metabolic deficiencies, and the metabolism of the DOACs has considerable variability among the various agents. Both rivaroxaban and apixaban undergo metabolic processing through the CYP 450 enzyme system. For volunteers receiving a single dose of 10 mg of rivaroxaban, patients with Child-Pugh class B hepatic impairment experienced reduced total body clearance of the drug and a 2.27-fold increase in total exposure secondary to reduced elimination and increased maximum concentration (C_{max}).⁴³ The authors postulated that this effect may have resulted from a decrease in hepatic CYP 450 enzyme activity.

Hepatic impairment can also impact agents that depend on hepatic excretion. DOACs with appreciable biliary excretion include apixaban and edoxaban (Table 2).⁹ A single-dose study in patients with mild or moderate hepatic impairment who received 15 mg of edoxaban did not have any increase in exposure or decrease in excretion of edoxaban.⁴⁴

4.1 Recommendations for hepatic impairment

As the quality of evidence is low in the studies listed above, it is difficult to make any conclusive recommendations about the use of DOACs in hepatic impairment. None of the DOACs have a restriction for use in mild hepatic impairment (Child-Pugh A) except in patients with known coagulopathy. Dabigatran and apixaban do not have restrictions in moderate hepatic impairment (Child-Pugh B), but none of the DOACs are recommended in patients with severe hepatic impairment (Child-Pugh C). Liver disease may result in reduced synthesis of procoagulant and anticoagulant factors, as well as cause deficiencies in platelet-derived hemostasis. Most patients with hepatic impairment are at an increased risk of

pharmacodynamic synergy between oral anticoagulation and disease state in regard to bleeding.⁹ To guide the use of DOACs in patients with hepatic impairment clinical judgment and assessment of the risk of bleeding with consideration for comorbidities, concomitant renal dysfunction and drug-drug pharmacokinetic/pharmacodynamic interactions must be utilized. It is prudent to discuss with the multidisciplinary transplant team the appropriate time to reinstitute anticoagulation after surgery, particularly if the patient has underlying hepatic impairment.

5 DRUG INTERACTIONS

As discussed previously, the metabolism of the DOACs has considerable variability among the various agents and is dependent on the CYP 450 enzyme system and P-gp efflux pump (Table 2). Drug-induced inhibition of the CYP 450 enzyme system results in an immediately increased concentration of active compounds metabolized by that specific enzyme. Drug-induced induction, considered a more gradual process, results in a decreased concentration of the CYP 450 substrate.^{45,46} Located on the apical membrane of enterocytes, hepatocytes, kidney proximal tubules, and endothelial cells of the blood brain barrier, P-gp is a membrane transport system responsible for the cellular efflux of substrates.⁴⁷ All of the DOACs are substrates of P-gp. There are a variety of agents considered inducers/inhibitors as well as substrates for P-gp and therefore must be taken into consideration when using and/or dosing most of the DOACs.⁴⁸

At present, there are no available randomized controlled studies directed at the evaluation of the effect of CNIs, mammalian target of rapamycin (mTOR) inhibitors, or antimetabolites on the metabolism, dosing, and effectiveness of any of the DOACs. A variety of information for safe and appropriate use of DOACs can be extrapolated from the prescribing information and available literature regarding strong CYP 3A4 inducers/inhibitors and P-gp inducers/inhibitors. As drug interactions are identified through postmarketing trials and clinical use, it is not uncommon to see descriptions and warnings of additional interactions added to package labeling. While there are a variety of comorbidities, drugs, and disease states that can affect the pharmacokinetic and pharmacodynamic disposition of DOACs, we briefly summarize below the available information pertaining to drug-drug interactions specifically important for their use in recipients of solid organ allografts.

5.1 Dabigatran drug interactions

Dabigatran etexilate, but not the active moiety, is a substrate of P-gp efflux pump. With no contribution from CYP 450 isoenzymes, strong inducers/inhibitors of the CYP 450 enzyme system, such as anticonvulsants, antifungals, and others, should be of little relevance for drug metabolism of dabigatran. Data from RE-LY found that concomitant use of dabigatran with either amiodarone or verapamil (P-gp inhibitors) increased dabigatran exposure but was not associated with differences in the event rate or bleeding.^{49,50} Although the US prescribing information does not suggest dose adjustments with P-gp inhibitors, the European Medicines Agency Summary of Product Characteristics lists concomitant treatment with cyclosporine, ketoconazole, itraconazole, and dronedarone as absolute contraindications for use with dabigatran.^{15,51} The US prescribing information does include

recommendations for dose reductions in patients with NVAF and impaired renal function when simultaneously administering concomitant P-gp inhibitors; it also recommends avoidance of dabigatran for treatment of VTE in the same patient population (see Table 1).¹⁵ Although little information is available about the effect of other P-gp inhibitors on dabigatran exposure, caution in its use is warranted in transplant recipients who are concomitantly treated with CNIs. Calcineurin inhibitors are known substrates of both CYP 450 3A4 and P-gp, as well as inhibitors of P-gp. Cyclosporine also inhibits the CYP 450 3A4 enzyme.⁵²

It should be noted that although clinical recommendations based on underpowered analysis cannot be made, in a single-center experience in nine heart transplant recipients immunosuppressed with CNIs and treated with dabigatran for atrial fibrillation, VTE, or atrial thrombus, changes in CNI dose were required.⁵³ When compared to anti-Xa inhibitors, patients prescribed dabigatran were more likely to require a decrease in tacrolimus dose during therapy ($P=.036$) and numerically had more major bleeding events ($P=.065$) when dabigatran was utilized with CNIs. However, appropriately powered studies are required to be able to make data-based clinical recommendations.

5.2 Rivaroxaban drug interactions

The prescribing information for rivaroxaban recommends avoiding administration of this drug together with dual-inhibitors of P-gp and CYP 450 3A4 as this may increase the exposure of rivaroxaban.²² Although ROCKET-AF excluded patients who received concomitant strong CYP 450 3A4 inducers/inhibitors, drug interaction studies have demonstrated a twofold increase in AUC of rivaroxaban when administered with strong dual P-gp/CYP 450 3A4 inhibitors. Less profound effects were noted with weak-to-moderate dual-inhibitors.^{19,54,55} Accordingly, strong dual-inhibitors should be avoided with rivaroxaban regardless of renal function.

While the package insert calls for avoidance of rivaroxaban with dual P-gp and CYP3A4 inhibitors, it is important to consider all other drugs used by the transplant recipient. As transplant recipients are frequently treated with many agents, other than CNIs, that can impact CYP3A4 and P-gp, this interaction is easily overlooked. Drug interaction software provided by Lexicomp® rates the interaction of rivaroxaban and calcineurin inhibitors with a risk rating of B, no action needed, contingent upon a number of notable dependencies including additional drugs/groups (CYP3A4 inhibitors), international labeling considerations, and renal function.⁵⁶ Micromedex Solutions® does not list any drug interaction between CNIs and rivaroxaban, and Clinical Pharmacology® rates only rivaroxaban and cyclosporine as a minor drug-drug interaction (Table 3).^{57,58} As the number of transplant patients requiring anticoagulation increases, the severity of these variations in the reported interaction may frequently influence clinical decisions and most recent studies and evaluations should be consulted for accurate reference frequently.

To our knowledge, there has only been one study which assessed the concentrations of rivaroxaban in patients treated with CNIs. Nine liver transplant patients on stable maintenance immunosuppression (cyclosporine, n=5 and tacrolimus, n=4) had trough concentrations of rivaroxaban monitored by a chromogenic anti-Xa activity assay. The mean

trough concentration of rivaroxaban was 131.7 ng/mL in patients treated concomitantly with cyclosporine vs 20.3 ng/mL in patients receiving tacrolimus. Three of five patients in the cyclosporine group reported episodes of mild bleeding vs only one patient receiving tacrolimus. Even with dose adjustments according to the patient's renal function, rivaroxaban exposure was increased in patients concomitantly receiving cyclosporine. It is important to note that patients in this study were maintained only at relatively low mean CNI trough concentrations (cyclosporine: 69 [$\pm$ 119.5] ng/mL; tacrolimus 3.4 [$\pm$ 14.4] ng/mL).⁵⁹ It is unknown whether CNIs' impact on rivaroxaban exposure would be more significant if target concentrations were considerably higher, as they usually are in the first 6–12 months following transplantation.

These findings parallel a previous study in renal transplant recipients which demonstrated that cyclosporine led to a substantial inhibition of P-gp activity as compared to tacrolimus or sirolimus. The authors suggest that the average 40-fold higher dose of cyclosporine is responsible for achieving inhibitory concentrations on both intestinal and hepatic P-gp.⁶⁰ Therefore, the rivaroxaban-cyclosporine interaction may be clinically more relevant than that of the rivaroxaban-tacrolimus drug interaction.

5.3 Apixaban drug interactions

Similar to rivaroxaban, apixaban is metabolized by both the CYP 450 enzyme system as well as P-gp. While phase III studies for apixaban excluded patients taking concomitant inhibitors of CYP 3A4/P-gp, the prescribing information recommends a 50% dose decrease when coadministered with drugs that are strong dual-inhibitors including ketoconazole, itraconazole, ritonavir, or clarithromycin.⁴¹ In a study with healthy volunteers, coadministration of apixaban with ketoconazole was associated with a 99% increase in AUC.⁶¹ For patients already prescribed a dose of 2.5 mg twice daily, coadministration should be avoided.⁴¹

5.4 Edoxaban drug interactions

Although edoxaban is eliminated via several pathways, P-gp is the primary route of its elimination.⁶² In ENGAGE AF-TIMI 48, patients treated concomitantly with strong P-gp inhibitors including verapamil, quinidine, or dronedarone required a 50% dose reduction in edoxaban.⁶³ This recommendation was based on a pharmacokinetic modeling study that supported reduction in the dose by half in patients with moderate renal insufficiency or in those treated with strong P-gp inhibitors including ketoconazole, erythromycin, azithromycin, quinidine, verapamil, and dronedarone.⁶⁴ This strategy aimed to provide patients with similar edoxaban exposure compared to those patients who did not receive P-gp inhibitor cotreatment and had normal renal function. This approach was later validated by a large population-based pharmacokinetic study including patients from all of the phase I atrial fibrillation studies.⁶⁵ However, subgroup analysis of the ENGAGE-TIMI 48 trial found that a greater number of strokes or systemic emboli occurred in patients on dose-reduced edoxaban presumably due to drug interactions, HR 2.17 (95% CI 0.66–7.06), although these findings were not statistically significant.⁶⁶ This may be partially explained by population pharmacokinetic analyses of edoxaban patients enrolled in the ENGAGE AF-TIMI 48 study which found that the 50% dose reduction in patients with low weight (< 60

kg), moderate renal impairment ($CL_{CR} < 50$ mL/min), or concomitant P-gp inhibitors led to 30% lower exposure to the drug than that found in patients without a dose reduction.⁶⁷ The prescribing information does not list a dose adjustment for edoxaban when used in NVAF with concomitant P-gp inhibitors; however, a maximum edoxaban dose of 30 mg daily should be used for VTE treatment when utilized with a concomitant P-gp inhibitor. This recommendation is based on the Hokusai-VTE study which did not suggest a difference in efficacy between reduced-dose and standard-dose edoxaban for VTE treatment.³⁹ The European Summary of Product Characteristics recommends a dose reduction of edoxaban by 50% for NVAF and VTE in patients who concomitantly receive cyclosporine.⁶⁸

5.5 Recommendations for drug interactions

It has been suggested that DOACs have few drug-drug interactions in patients studied in clinical trials. However, little is known about the clinical use of these drugs and their drug interactions in transplant recipients. Clinicians should be cautious when using DOACs in solid organ transplant recipients due to fluctuations in renal function, polypharmacy with concomitant P-gp inhibitors, and the lack of clinical data on interactions with CNIs, mTORs, and certain antifungals. It cannot be sufficiently emphasized that all medications, concurrent comorbidities, and renal function must be taken into consideration prior to use of DOACs.

6 MANAGEMENT OF DOACS AT TIME OF TRANSPLANTATION SURGERY

An important consideration with the use of DOACs for anticoagulation in solid organ transplantation candidates is the need for reversal prior to transplantation or any urgent surgery. Recommendations for warfarin suggest stopping it for 5 days before a planned operation or utilizing a reversal agent to facilitate urgent surgical procedures.⁶⁹ Historically, fresh-frozen plasma (FFP) and low-dose 3-factor prothrombin complex concentrates (3F-PCCs) have been utilized for warfarin reversal prior to heart transplantation.⁷⁰ More recently, with the approval of Kcentra®, 4-factor PCCs have been utilized for warfarin reversal prior to heart transplantation, providing a reduction in total volume of blood products needed, without reported thromboembolic complications.⁷¹ Similar strategies have been utilized for other types of solid organ transplantation. The introduction of the DOACs makes utilization of these recommendations difficult and ineffective, as discussed below.

The half-lives of DOACs vary considerably based on age, renal and hepatic function, and drug interactions.^{3,72} Recommendations for discontinuation of each specific agent are based on the medication half-life which is valuable in patients who have a scheduled date of surgery (Table 3). Unfortunately, there are no current studies that describe the estimated half-lives in patients with end-stage organ failure; accordingly, these recommendations should be applied on a patient-specific basis. For low-bleeding-risk transplant operations, discontinuation of the DOACs approximately two half-lives prior to any surgical intervention is considered relatively safe.^{3,73,74}

Utilization of DOACs in patients awaiting deceased-donor transplantation requires caution as are the concern prior to any urgent major operation. Due to the sporadic availability of donor organs, patients may be called for transplantation without the opportunity to discontinue anticoagulation beforehand. Furthermore, the duration and invasiveness of the

operation should be considered in regard to bleeding risk at the time of transplant or any other operation. With DOACs, there is the uncertainty of the degree of anticoagulation, as commonly available assays to measure hemostasis are unreliable. While activated partial thromboplastin time (aPTT) may be helpful in evaluating coagulation status with dabigatran, and prothrombin time (PT) with Xa inhibitors, both tests are unreliable to predict the current state of coagulopathy and they do not correlate well with plasma drug concentrations.^{75–78} More sensitive assays, with better correlation, such as ecarin clotting time and thrombin time, may not be available for immediate clinical use. More recently, a linear relationship between anti-Xa activity and drug concentration for Xa inhibitors has been demonstrated.^{79,80} This potentially makes this approach useful at the time of transplant or other operation because it may predict degree of coagulopathy or in the post-transplantation setting may be useful as a monitoring strategy. Guideline recommendations and expert opinion suggest emergency surgery or invasive procedures with a high-risk for bleeding should be delayed as long as possible or for at least 1–2 elimination half-lives (approximately 13–24 hrs). As age, renal and hepatic function, and drug interactions play a role in determining the half-life of these agents, surgery may need to be delayed for as long as 5 days, based on discontinuation of the agent alone.^{73,74}

Dabigatran is the only DOAC that can be removed by hemodialysis. In the setting of kidney transplantation, this is potentially useful for patients who present for transplant with available access to undergo hemodialysis prior to transplantation. Of note, hemodialysis removes approximately 60% of the plasma concentration of dabigatran in 2–3 hours.^{4,12} Clinicians should be aware that due to the lipophilicity of dabigatran, it concentrates very well within tissue; a drug rebound effect has been observed in which a redistribution of dabigatran from the extravascular to the intravascular space occurs within a few hours after hemodialysis.⁸¹ Repeat hemodialysis sessions ensure the risk of bleeding has been minimized; this may be undesirable, but necessary, in the immediate post-transplant setting. Antifactor Xa inhibitors are appreciably protein bound and therefore are not dialyzable.

The recent approval of idarucizumab, a monoclonal antibody fragment specific for dabigatran, may provide a therapeutic option for reversal of anticoagulation prior to transplantation or any operation. Idarucizumab is approved for the reversal of dabigatran-induced coagulopathy in patients with life-threatening or uncontrolled bleeding and in patients requiring emergent/urgent procedures. This new reversal agent adheres to the thrombin-binding site of dabigatran rendering it inactive. The idarucizumab-dabigatran complex is then renally excreted.⁸² While it has not been studied in organ transplant recipients, renal impairment does not alter its efficacy, and no dosing adjustments are required. Clinicians should be cautious about preferentially utilizing dabigatran in the post-transplant setting based solely on the availability of a reversal agent. Urgent reversal of dabigatran in patients with serious bleeding or requiring an urgent procedure results in complete reversal of the anticoagulant effect, but may not result in immediate hemostasis. The benefit of this agent on overall clinical outcomes is currently unknown.⁸³ The use of idarucizumab in place of hemodialysis is intriguing in organ transplant candidates prior to surgery. Additional information about recurrent use of idarucizumab will be critical before its use prior to transplantation, as well as information about its repeat use, due to the potential for the formation of antibodies targeted against idarucizumab.⁴

Reversal agents for Xa inhibitors are not currently available. In general, the use of activated clotting factors such as factor eight inhibitor bypassing activity (FEIBA), recombinant activated factor seven (rFVIIa), and inactivated 4F-PCCs have been largely ineffective for reversal of DOACs in healthy volunteers.^{3,84,85} While reports of successful reversal of dabigatran with FEIBA exist, caution should be employed when using this agent for reversal due to a potential increased risk of thrombosis.⁸⁶ The primary indication for the use of DOACs and the thrombogenic nature of the transplant surgery should be taken into consideration prior to utilizing these reversal modalities. Additionally, it is important to note that fresh-frozen plasma (FFP) is not effective for reversing the DOACs.⁴

There is currently one reported case describing the use of DOAC prior to bilateral lung transplantation, without reversal beforehand. The authors utilized rotational thromboelastography (ROTEM®) traces before, during, and after surgery, in addition to standard assays of hemostasis, to transplant a patient who took 20 mg of rivaroxaban 30 hours prior to surgery. No blood products, coagulation factors, or reversal agents were administered, and no bleeding events were reported.⁸⁷ This case highlights the potential for no reversal at the time of transplant surgery, albeit under controlled conditions. The reinitiation of DOACs postsurgery should be started when hemostasis has been effectively achieved, with approval of the transplant surgeon.

7 SYSTEMIC ANTICOAGULATION IN IMMEDIATE POST-TRANSPLANT PERIOD

Ischemia-induced injury to the kidney both during the procurement period and transplant surgery can lead to temporarily reduced graft function in the immediate post-transplant period, with (DGF) or without (slow graft function) the requirement for hemodialysis in 25% of deceased-donor recipients and 3%–5% of living-donor recipients.^{88,89} Recipients of nonrenal solid organ transplants are also at risk for acute kidney injury (AKI) resulting from cardiac or hepatic failure, prolonged surgery, and nephrotoxic effects of immunosuppression with incidence of AKI being 25%, with 8% of patients requiring renal replacement therapy.⁹⁰ Therefore, use of DOACs in the immediate post-transplant period can be challenging. Also, most episodes of acute rejection of kidney allografts occur within the first 6 months after transplantation, with many such episodes occurring early after surgery, necessitating a higher dose of CNIs and an emergent biopsy. Given the unpredictable renal function and drug-drug interaction and the potential need for an immediate reversal of anticoagulation prior to biopsy, it may be reasonable to avoid the use of DOACs in the immediate post-transplant period until a stable renal allograft function has been achieved, especially in deceased-donor kidney transplants and in high-immunological risk kidney transplants.

8 CONCLUSION

DOACs are an alternative option to warfarin for anticoagulation in the general population for selected indications. These agents do not require monitoring and are potentially safer than and at least as efficacious as warfarin. Despite these benefits, there are specific limitations that should also be taken into consideration before using DOACs in solid organ transplant

recipients. Most importantly, there is limited information regarding the use of DOACs in patients with renal impairment and in those with fluctuating renal function. Most of the available data is extrapolated from single-dose studies that do not accurately represent steady-state conditions. Drug-drug interactions are also very important, especially in transplant recipients, as all of the DOACs are substrates of P-gp, with rivaroxaban and apixaban also being substrates of CYP 450 3A4 and at present, almost all allograft recipients are maintained by CNIs, receive antihypertensives and frequently antifungal drugs. Finally, data regarding the use of currently available or investigational antidotes will be needed prior to widespread use of these agents in this population. Currently, the best recommendation for the use of DOACs at the time of surgery involves discontinuation of the agent and delaying surgery based on its estimated half-life in any specific patient. In the immediate post-transplant period, DOACs should be avoided until stable renal function has been established. The risks and benefits of the use of DOACs in solid organ transplant recipients should be weighed prior to the introduction of the agent in this highly distinct patient population.

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FIGURE 1.

Coagulation cascade. Oral direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) prevent the formation of clot by binding to activated factor Xa in the coagulation cascade. Oral direct thrombin inhibitors (dabigatran) inhibit the formation of clot by directly binding to activated factor IIa or thrombin

TABLE 1

Indications and dosing based on renal function

Indications and dosing	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Nonvalvular atrial fibrillation	CLcr >30 mL/min: 150 mg twice daily CLcr 15–30 mL/min: 75 mg twice daily CLcr <15 mL/min or on dialysis: no recommendations provided	CLcr >50 mL/min: 20 mg once daily with the evening meal CLcr 15–50 mL/min: 15 mg once daily with the evening meal CLcr <15 mL/min: avoid use	5 mg twice daily 2.5 mg twice daily in patients with at least two of the following characteristics: age ≥80 y, body weight ≥60 kg, serum creatinine ≤1.5 mg/dL	Do not use in patients with CLcr >95 mL/min CLcr 50–95 mL/min: 60 mg once daily CLcr 15–50 mL/min: 30 mg once daily CLcr <15 mL/min: avoid use
Treatment of DVT and PE Reduction in the risk of recurrence of DVT and PE	CLcr >30 mL/min: 150 mg twice daily CLcr ≤30 mL/min or on dialysis: dosing recommendations not provided	CLcr ≥30 mL/min: 15 mg twice daily with food, for first 21 d, and then transition to 20 mg once daily with food, for remaining treatment CLcr <30 mL/min: avoid use	10 mg twice daily for the first 7 d of therapy After 7 d, the recommended dose is 5 mg taken orally twice daily	CLcr >50 mL/min: 60 mg once daily following 5 to 10 d of initial therapy with a parenteral anticoagulant CLcr 15–50 mL/min: 30 mg once daily CLcr <15 mL/min: avoid use
Prophylaxis of DVT and PE following hip replacement surgery	CLcr >30 mL/min: 110 mg for first day and then 220 mg once daily CLcr ≤30 mL/min or on dialysis: dosing recommendations cannot be provided	CLcr ≥30 mL/min: 10 mg once daily for 35 d CLcr <30 mL/min: avoid use	Hip replacement: 2.5 mg twice daily for 35 d	Not indicated
Prophylaxis of DVT and PE following knee replacement surgery	Not indicated	CLcr ≥30 mL/min: 10 mg once daily for 12 d CLcr <30 mL/min: avoid use	2.5 mg twice daily for 12 d	Not indicated

CLCR, creatinine clearance; DVT, deep-vein thrombosis; PE, pulmonary embolism.

TABLE 2

Pharmacokinetics

Pharmacokinetics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Absorption	Bioavailability 3%–7%, pH dependent	Bioavailability (10 mg tablet) 80%–100%; 20 mg tablet in fasted state is 66% and increased when taken with food	Bioavailability 50%	Bioavailability 62%
Distribution	34%–35% plasma protein binding; volume of distribution 60–70 L	92%–95% plasma protein binding; volume of distribution 50 L	87% plasma protein binding; volume of distribution 21 L	Plasma protein binding 55%; volume of distribution 107 L; biphasic distribution
Metabolism	Dabigatran etexilate rapidly converted to dabigatran by esterase catalyzed hydrolysis	Oxidative degradation catalyzed by CYP 3A4/5 and CYP 2J2 and hydrolysis	25% recovered in urine and feces as metabolites; metabolism via CYP3A4, 1A2, 2C8, 2C9, 2C19, and 2J2	Unchanged edoxaban is the predominant form in plasma; minimal metabolism via hydrolysis, conjugation, and oxidation by CYP3A4
Excretion	Renal (85%), T _{1/2} 10–11 h; 61%–68% of systemic dabigatran removed by dialysis	33% excreted unchanged in the urine via active tubular secretion and glomerular filtration (5:1 ratio); substrate of P-gp and ABCG2 (Bcrp) transporter proteins	Renal excretion 27%; T _{1/2} 12 h; substrate of P-gp and Bcrp	Unchanged drug in the urine (50%) and biliary/intestinal excretion (50%); T _{1/2} 10–14 h

TABLE 3

Elimination half-life based on renal function

Renal insufficiency	Half-life (h)
Dabigatran ^{3,12,72}	
CLcr >80 mL/min	13.8
CLcr 50–79 mL/min	16.6
CLcr 30–49 mL/min	18.7
CLcr <30 mL/min	27.5
Hemodialysis	34.1
Rivaroxaban ^{3,23,24,72}	
CLcr >80 mL/min	8.3
CLcr 50–79 mL/min	8.7
CLcr 30–49 mL/min	9.0
CLcr <30 mL/min	9.5
Hemodialysis	12–13
Apixaban ^{3,33,34,72}	
CLcr >80 mL/min	15.1
CLcr 50–79 mL/min	14.6
CLcr 30–49 mL/min	17.6
CLcr <30 mL/min	17.3
Hemodialysis	12.5/12.7 ^a
Edoxaban ^{37,38}	
CLcr >80 mL/min	8.6
CLcr 50–79 mL/min	8.6
CLcr 30–49 mL/min	9.4
CLcr <30 mL/min	16.9
Hemodialysis	10–14 ^b

^a Estimated half-life was 12.5 h for patients given apixaban 5 mg 2 h before dialysis and 12.7 h for patients given 5 mg of apixaban following a 4-hour hemodialysis session.

^b Parent molecule T_{1/2} 10 h. M-4 metabolite (pharmacologically active) T_{1/2} 14 h.

TABLE 4

Drug-drug interaction severity rankings

	Cyclosporine				Tacrolimus			
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Lexicomp ^a	Category D P-Glycoprotein/ ABCBI inhibitors may increase serum concentrations of the active metabolite(s) of dabigatran etexilate Severity major Reliability rating fair	Category B P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of rivaroxaban Severity minor Reliability rating fair	Category B P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of apixaban Severity minor Reliability rating fair	Category D P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of edoxaban Severity major Reliability rating fair	Category D P-Glycoprotein/ ABCBI inhibitors may increase serum concentrations of the active metabolite(s) of dabigatran etexilate. Severity major Reliability rating fair	Category B P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of rivaroxaban Severity minor Reliability rating fair	Category B P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of apixaban Severity minor Reliability rating fair	Category D P-Glycoprotein/ ABCBI inhibitors may increase the serum concentration of edoxaban. Severity major Reliability rating fair
Micromedex ^b	Major Concurrent use of cyclosporine and dabigatran may result in increased dabigatran exposure	No interaction	Major Concurrent use of apixaban and selected P-gp inhibitors may result in increased risk of bleeding	No interaction	No interaction	No interaction	No interaction	No interaction
Clinical pharmacology ^c	Level 2 Dabigatran etexilate may have its serum concentration increased by cyclosporine	Level 4 Rivaroxaban may have its serum concentration increased by cyclosporine	No interaction	Level 3 Cyclosporine may increase the serum concentration of edoxaban	Level 3 Dabigatran etexilate may have its serum concentration increased by tacrolimus	No interaction	No interaction	No interaction
Package insert	Not listed	Not listed	Not listed	Listed Increased area under the curve and C _{max}	Not listed	Not listed	Not listed	Not listed

^a Lexi-comp—Category A: no known interaction; Category B: no action needed; Category C: monitor therapy; Category D: consider therapy modification; Category X: avoid combination.

^b Micromedex—Contraindicated: The drugs are contraindicated for concurrent use; Major: the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects; Moderate: the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy; Minor: the interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy; Unknown: unknown.

^c Clinical pharmacology—Level 1 (Severe—avoid using these drugs together): The use of these medications together is contraindicated. Rare exceptions may exist; Level 2 (Major): The use of these medications together may be contraindicated in a select group of patients. Further therapy and/or an alteration in therapy may be necessary to avoid or limit the potential for interaction. The patient should be monitored for possible manifestations of the interaction; Level 3 (Moderate): The use of these medications together may result in unintended clinical effects. Depending on the clinical situation,

alterations in therapy may be required. The patient should be monitored for possible manifestations of the interaction; and Level 4 (Minor): The use of these medications together does not usually result in clinically significant interactions. Alterations in therapy or monitoring are not usually required.

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