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Review Article Title:
Drug Interactions between Direct-Acting Oral Anticoagulants and Calcineurin Inhibitors during Solid Organ Transplantation: Considerations for Therapy

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Abstract

Introduction: There is a high incidence of venous thromboembolism (VTE) in solid organ transplant recipients. The safety and efficacy of direct-acting oral anticoagulants (DOAC) have been well established in clinical practice for the prevention and treatment of VTE in broad populations. However, the management of VTE in the setting of solid organ transplantation remains a challenge to clinicians due to limited evidence of DOAC usage with calcineurin inhibitors.

Areas covered: The current literature available on the pharmacokinetic-pharmacodynamic interaction between DOACs and calcineurin inhibitors is presented. A comprehensive review was undertaken using PubMed, Embase, drug product labeling, and drug product review conducted by the US Food and Drug Administration using Drugs@FDA. The potential for mitigation strategies and clinical management using extant knowledge is explored.

Expert Opinion: Immunosuppression therapy is necessary to prevent graft rejection by the host. The sparsity of data together with the lack of well-designed prospective studies of DOAC use in solid organ transplant recipients presents a unique challenge to clinicians in determining the clinical relevance of possible drug interactions. Existing evidence suggests that with attention to concomitant drug use and renal function, the co-administration of DOACs and calcineurin inhibitors is safe and effective.

Keywords: direct oral anticoagulants, DOAC, cyclosporine, tacrolimus, anticoagulation, venous thromboembolism, apixaban, rivaroxaban, dabigatran, warfarin

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Article Highlights

• The calcineurin inhibitors, cyclosporine and tacrolimus, are commonly used in maintenance immunosuppression regimens to prevent graft rejection following solid organ transplant. Cyclosporine may have a higher likelihood of inhibiting drug metabolizing enzymes and transporters compared to tacrolimus.

• Direct oral anticoagulant (DOAC) clinical trials often excluded those on either cyclosporine or tacrolimus.

• Identifying intrinsic and extrinsic variabilities in the pharmacokinetics-pharmacodynamics in solid organ transplant recipients may balance the risks of bleeding while maintaining adequate anticoagulation.

• The Cockcroft-Gault formula using ideal body weight is used for dosing adjustments for apixaban and edoxaban while actual body weight is used to adjust dabigatran and rivaroxaban.

• While limited, pharmacokinetic-pharmacodynamic and outcomes evidence suggests safe and effective use of DOACs together with calcineurin inhibitors.

• Anti-Factor Xa monitoring is not standardized and is not helpful in dose selection.

• Direct oral anticoagulant use should be avoided in the immediate post-operative period and considered only after there is stability of renal and hepatic function and when bleeding risk has stabilized.

• Dose adjustment should not be made in the setting of acute thrombosis. After at least three months of therapy, intrinsic and extrinsic factors may inform the use of switching to attenuated dose for secondary thromboprophylaxis.
1. Introduction

Solid organ transplantation offers a lifesaving option to patients with end-stage kidney, liver, heart, or lung disease. Between 1987 and 2012, 2 million life-years were saved by solid organ transplantation in the United States.[1] Acute and chronic immunosuppression therapy has been established as the cornerstone to prevent graft rejection, subsequent loss of the transplanted organ, and overall survival of the patient. Management of the transplant recipient using immunosuppression therapy is multi-modal where most immunosuppressive regimen include the calcineurin inhibitors (CNI) cyclosporine (CsA) and tacrolimus.[2-4]

Following solid organ transplantation, the incidence for venous thromboembolism (VTE) was 5%, 14%, 29%, and 34%, for patients that underwent liver, renal, lung and heart transplant, respectively.[5] Although the reasons for higher incidence is not defined, factors including thrombophilic states (e.g. protein C, S or antithrombin III deficiency), clinical (e.g. diabetes mellitus, systemic lupus erythematosus), or donor-recipient (e.g. donor/recipient atheroma) have been proposed.[6] A thrombogenic state induced by immunosuppressive therapy has also been proposed based on in-vitro and clinical observations, however studies in renal transplant recipients remain contradictory.[7,8] Aside from the thrombogenic risk following organ transplant, risks for VTE are also inherent in patients who are greater than 40 years-old, immobile, or obese.[9]

The vitamin K antagonist warfarin has been the historical standard of care for the oral treatment of VTE. In solid organ transplant recipients, most protocols involve administering a parenteral anticoagulant (heparin or low molecular weight heparin) followed by warfarin maintenance for 3-6 months.[5] In the general patient population, the direct acting oral anticoagulants (DOAC) are at least as efficacious as warfarin. They have fewer drug interactions, a wider therapeutic window, and a fixed-dose regimen without continuous monitoring of the coagulation profile. While these characteristics are
particularly appealing for use in clinical care, specific guidance in transplant patients is lacking since this population has been excluded from clinical trials of DOACs.

Calcineurin inhibitors block several drug transporters and metabolizing enzymes. Direct oral anticoagulants are substrates of specific drug transporters and metabolic enzymes involved in the absorption and elimination of drugs. Given the incidence of VTE following solid organ transplant and the prevalent use of CNIs in maintenance immunosuppressive regimens, the use of DOACs together with CNIs may result in a drug-drug interaction (DDI). These drug interactions are most impactful at treatment doses for labeled indications of venous thromboembolic disease or atrial fibrillation, rather than the lower doses used for primary prevention of venous thromboembolic disease.

2. Maintenance Pharmacotherapy in the Solid Organ Transplant Recipients: Calcineurin Inhibitors

2.1. Tacrolimus

Tacrolimus is a macrolide antibiotic isolated from *Streptomyces tsukubaensis*. Its mechanism involves complexation with the immunophilin FK-binding protein which produces immunosuppression by downstream inhibition of cytokine production and a loss of T-lymphocyte activation, proliferation, and response. Tacrolimus is part of maintenance immunosuppression in over 80% of kidney, pancreas, liver, intestine, heart, and lung transplant recipients and is indicated for the prophylaxis of organ rejection in kidney, liver and heart transplant.[10,11] Following oral administration, tacrolimus is extensively metabolized by cytochrome P450 (CYP) CYP3A4 and CYP3A5 and is a substrate for permeability glycoprotein (P-gp). It is unclear whether tacrolimus has the potential to inhibit drug metabolizing enzymes or efflux transporters in humans. While in-vitro and non-human in-vivo models have described a possible inhibitory effect on CYP3A4 and P-gp,[12] the pharmacokinetic impact of tacrolimus and other CYP3A and P-gp substrates in healthy volunteers is likely to be clinically irrelevant in patient populations.[13,14]
2.2. Cyclosporine

Isolated from the fungal species *Tolypocladium inflatum* found in soil, cyclosporine was originally developed as an antifungal medication. Reduction in T-lymphocyte activity and immunosuppression by CsA occurs through the binding and complex formation with cyclophilin that results in downstream transcriptional inactivation of various interleukins and cytokines. Cyclosporine is extensively metabolized by CYP3A4 in the intestine and liver and is a P-gp substrate.[15] In addition, CsA is a potent inhibitor of intestinal and hepatic efflux transporters including breast cancer resistance protein (BCRP) and P-gp; hepatic uptake transporters such as organic anion transporting polypeptide (OATP); and CYP3A4. Drug metabolism by 3A4 takes place in liver and pre-systemically in the intestine. Due to its activity at the level of the intestines and liver, CsA may pose clinically relevant DDIs as both the victim and perpetrator drug.

Cyclosporine is indicated for the prophylaxis of organ transplant rejection following kidney, liver, and heart transplantation.[16,17] Although tacrolimus appears to be the favored CNI in the US and Asia, there is still considerable global use of CsA.[18,19] Dose-dependent acute nephrotoxicity and chronic nephropathy from CsA exposure is a significant adverse event contributing to renal dysfunction following renal or non-renal transplant.

3. Pharmacokinetics Following Transplantation: Absorption, Distribution, Metabolism, & Elimination

A number of physiological changes occur after transplantation which impact drug disposition (figure 1). The major transplanted organs have a direct or indirect role in drug absorption, distribution and elimination. These changes are dynamic and can occur immediately following transplantation. Changes in gastric pH and emptying, gastrointestinal motility, incidence of diarrhea, bile dysfunction, and differential expression of drug efflux transporters following transplantation can alter absorption of drugs into the systemic circulation.[20-26] Drug distribution into tissues or free-fraction availabilities have also been shown to be impaired due to fluctuations in body weight or alterations in protein binding.[27-34]
Lastly, drug elimination may be altered due to higher hepatic blood flow, upregulation of drug metabolizing enzymes, changes in bile flow, or decline in renal function.[35-40]  

### 4. Intrinsic and Extrinsic Factors Affecting DOAC Disposition in Solid Organ Transplant Recipients

No formal studies have investigated the PK of DOAC therapy in solid organ transplant recipients. Variability derived from intrinsic (altered protein binding, obesity, gastric motility) and extrinsic (DDI) factors following transplantation may contribute to significant inter-recipient variability in the exposure and the efficacy or safety response to DOACs. For the purposes of this review, extrinsic factors—mainly those contributed from DDIs—will be discussed in detail. Drug metabolizing enzymes and transporters play an important role in the disposition of drugs. The drug transporters, P-gp and BCRP, are commonly expressed in the intestinal epithelia where their expression limits entry of therapeutic drugs.[41] In excretory organs, drug transporters function to remove endogenous and xenobiotic compounds. Therefore, efflux mechanisms can result in pharmacokinetic DDIs between CNI and DOACs during the absorption or elimination phases. For CsA an interaction in the intestine can be considerable, since a large magnitude of the delivered dose is in unbound form compared to delivery to the liver. In the intestines, the inhibition of P-gp and BCRP by CsA was estimated using physiologically based pharmacokinetic modeling to be up to 80% and 67%, respectively.[42] Moreover, up to 97% of intestinal CYP3A4 is inhibited following a single oral dose. [42] In the intestines, P-gp, BCRP and CYP3A4 activity returns to maximal activity within 4-6 hours after discontinuing CsA. Within the liver, P-gp, BCRP, and CYP3A4 enzyme activity is estimated to be reduced by 4%, 2%, and 26%, respectively.[42] Tacrolimus has been shown to share common inhibitory mechanisms as CsA with significantly less inhibition potential. For stabilized renal transplant patients receiving tacrolimus, intestinal and hepatic CYP3A4 and P-gp activities are insignificant. In contrast, the activity of intestinal CYP3A4 were starkly elevated in patients on CsA together with significant reductions in intestinal and hepatic P-gp.[43] These findings enforce the differential
effects of CsA and tacrolimus on drug metabolizing enzymes and transporters for which a greater variation in drug exposure is anticipated for drugs co-administered with CsA. Clinically, the magnitude of tacrolimus inhibition on CYP3A4 and P-gp is expected to be minimal at therapeutic drug doses. [12,43]

It is important to keep in mind that although the magnitude of inhibition of transporters and enzyme may appear large, differential expression along the length of the small intestine and lower abundance of protein relative to the liver may minimize drug interaction potential.[44] In the case of the DOACs, clinically relevant DDIs may result at the level of absorption (i.e. the intestines) or elimination (i.e. renal or non-renal routes) when given together with CsA or tacrolimus. All DOACs are substrates of drug efflux transporters and, with the exception of dabigatran, substrates for CYP3A4. Use of P-gp or CYP3A4 inhibitors, especially CsA or tacrolimus, were mostly excluded from pivotal trials in patients during the clinical development of each DOAC.[45-48] While information related to the clinical relevance of the DDI in patient populations is limited, available PK studies in healthy volunteers may provide insight in the magnitude of change and its relationship to safety and efficacy. Table 1 summarizes the extrinsic factors relating to DDIs for DOACs and their respective exposure and peak concentration changes in the presence of their substrate transporter and/or enzyme inhibitor. In the absence of a dedicated CsA or tacrolimus study, we reference available substrate transporter and/or enzyme inhibitors that share the same mechanistic pathways to provide insight to the magnitude of changes in the exposure and peak concentrations.

4.1. Dabigatran

Dabigatran etexilate directly and reversibly inhibits thrombin, rather than reducing the production of vitamin K dependent clotting factors.[49] Dabigatran etexilate is a prodrug that is orally absorbed with an absolute bioavailability of approximately 3-7%. Conversion to the active moiety, dabigatran, is independent of CYP isoenzymes and is formed following hydrolysis by carboxylesterases. It is the prodrug that is a substrate of P-gp rather than the active moiety, which may account for its low
bioavailability and variable PK. In addition, changes in gastric pH and intestinal motility have also contributed to the observed differences in PK following surgery.[50] The volume of distribution is moderate at 60 liters with an in-vitro plasma protein binding of 35% across therapeutic concentrations. Dabigatran, but not dabigatran etexilate, is detectable in systemic circulation following oral administration. Dabigatran metabolism is minimal and it is not a substrate or inhibitor of CYP450 enzymes. Renal clearance is the major route of dabigatran drug elimination representing 80% of the total clearance. Following intravenous dosing, greater than 80% of the dose was recovered in the urine compared to only 7% after oral administration. The remaining 86% of orally dosed dabigatran was recovered in the feces most likely due to incomplete absorption of DE. Dabigatran elimination half-life is 12-17 hours.

Dabigatran etexilate exhibits predominately P-gp dependent transport, demonstrated by in-vitro inhibition studies using verapamil as a P-gp inhibitor.[51] In the presence of CsA, a P-gp and BCRP inhibitor, greater than 80% of efflux was inhibited as observed using the same in-vitro Caco-2 permeability model. These results implicate CsA as a potential perpetrator for clinical in-vivo drug interactions following co-administration with dabigatran etexilate. To date, no dedicated in-vivo clinical studies have been conducted evaluating the DDI between dabigatran etexilate co-administered with either CsA or tacrolimus. P-gp inhibition may be time-dependent and influenced by the timing of a co-administered perpetrator. Following multiple oral doses of verapamil in healthy volunteers, total dabigatran exposure and peak concentration increased by 54% and 63% after a single-oral 150 mg dabigatran etexilate dose 1 hour after verapamil, respectively.[52] When dabigatran etexilate was given 2 hours prior to verapamil, exposure and peak concentration increased by 18% and 12%, respectively. Considering the inhibition activity of CsA in-vitro, results from co-administered verapamil alone may not satisfy the clinical relevance of both P-gp and BCRP inhibition. Insightful results based on in-silico modeling using ritonavir, a dual P-gp and BCRP inhibitor, have estimated exposure and peak concentration increases of approximately 25% and 16%, using a simulated 200 mg twice-daily regimen, respectively.[53]
Dabigatran transporter mediated DDIs are best assessed using data obtained in healthy volunteers using the broad ATP-binding transporter and CYP3A4 inhibitor ritonavir.[54] Following multiple-oral doses of ritonavir 100 mg daily, single-dose dabigatran exposure was increased by 15% when administered simultaneously and reduced by 29% when dabigatran etexilate was administered 2 hours prior to dosing ritonavir. These observations likely confirm the time-dependency of co-administered perpetrator drugs on the PK profile of dabigatran. P-gp inhibition and renal dysfunction are both independent factors that enhances the exposure of DE.

In patients receiving dabigatran etexilate for treatment and prevention of VTE, there is no dosage adjustment or contraindication to P-gp inhibitors so long as patients have a creatinine clearance greater than 50 mL/min.[55] These recommendations are intuitive considering the most important factor influencing dabigatran exposure is renal clearance. Therefore, the use of dabigatran etexilate is completely contraindicated in those with creatinine clearances less than 50 mL/min. Despite these results, the U.S. labelling for CsA suggests avoiding co-administration with dabigatran etexilate altogether regardless of renal function.[16,17] Drug-drug interactions involving dabigatran etexilate may be restricted to only intestinal P-gp rather than other sites. In addition, BCRP and CYP3A4 liability is not a general concern as witnessed from in-vitro permeability models and clinical DDI studies using the P-gp, BCRP and CYP3A4 inhibitor, ritonavir. Based on these findings, dabigatran is a suitable choice in transplant patients co-prescribed CsA or tacrolimus, so long as estimated creatinine clearance is > 50 ml/min. As the risk of higher exposures and subsequent bleeding risk will be low in those with creatinine clearances greater than 50 mL/min using a CNI, caution should be enforced especially during periods of fluctuating physiology during the post-transplant period. A shorter acting parenteral anticoagulant should be considered before dabigatran until renal function stabilizes and the bleeding risk has declined. In the setting of acute VTE, the label outlines at least five days of treatment be with a parenteral agent (heparin or enoxaparin) before transitioning to dabigatran etexilate.
4.3. Rivaroxaban

Rivaroxaban is a direct oral factor Xa (FXa) inhibitor approved by the FDA for the treatment and prevention of recurrent VTE and reducing risk of stroke in atrial fibrillation.[56] Absolute bioavailability is dose dependent where almost complete absorption (80 to 100%) is achieved at the 10 mg dose but reduced to 66% for the 20 mg dose. The site of absorption is primarily in the proximal small intestine where peak concentrations are observed 2 to 4 hours following oral intake. Rivaroxaban is highly bound to plasma proteins with a steady-state volume of distribution of 50 liters. Approximately two-thirds of the administered dose is subjected to metabolic transformation through CYP3A4/5 and CYP2J2 metabolism where it accounts for 18% and 14% of the total rivaroxaban elimination, respectively. No major active circulating metabolites in plasma are present following administration. The remaining one-third of the administered dose is eliminated renally as unchanged drug where 30% is removed through active renal secretion and the remaining 6% through glomerular filtration. The elimination half-life in healthy subjects is 5 to 9 hours whereas elderly subjects had prolonged half-lives ranging from 11 to 13 hours. Rivaroxaban is a substrate for the efflux transporters P-gp and BCRP and has equal affinity for both transporters.[51]

Based on pooled phase I results, the impact of age, race, renal and hepatic insufficiency were observed to influence the area under the concentration-time curve (AUC). Healthy elderly subjects older than 75 years of age have greater than 40% higher exposures, primarily due to a decline in renal function and non-renal rivaroxaban clearance.[57]. A dose-reduction strategy is recommended to account for renal function based on creatinine clearance.[56]

Although there is no dedicated DDI study with CsA, similar perpetrator inhibitors- such as erythromycin- sharing the same inhibitory pathway may offer an insight in the magnitude of interaction.[58] Erythromycin is a combined P-gp and moderate CYP3A4 inhibitor which shares the same characteristic as CsA. Following multiple-doses of erythromycin, the AUC and peak concentrations are
increased by 34% and 38% after a single-dose of rivaroxaban. Similarly, the AUC and Cmax are increased by 42% and 28% following co-administration with the combined moderate CYP3A4 and BCRP inhibitor fluconazole. These individual elevations in the AUC and peak concentrations alone do not warrant a dosage change or contraindication as these values fall within the ranges observed of drug use in the general patient population. Although one intrinsic or extrinsic factor alone does not preclude the use of rivaroxaban, the presence of greater than one factor may present a complex drug-drug and drug-disease interaction producing a clinically significant increase in rivaroxaban exposure. When accounting for renal function, age, and DDI with erythromycin, increase in the AUC by 1.9, 2.4, and 2.6-fold were predicted in younger patients with mild, moderate, or severe renal impairment while co-administered erythromycin, respectively.[59] The impact from older age with erythromycin (55-65 years old) predicted a 2.5, 2.9 and 3-fold increase in the AUC in individuals with mild, moderate or severe renal impairment, respectively. Although these results should not be extrapolated to those using CsA or tacrolimus, cautious monitoring and careful clinical consideration for rivaroxaban use should be practiced especially in older patients with reduced renal function.

### 4.4. Edoxaban

Edoxaban is a selective inhibitor of FXa indicated for the risk reduction of stroke and emboli in non-valvular atrial fibrillation and treatment of VTE.[60] Like dabigatran but unlike the other FXa inhibitors, edoxaban is labeled to be started after 5 to 10 days of parenteral anticoagulation in the treatment of acute VTE. Edoxaban demonstrates pH-dependent solubility where optimal dissolution is achieved in the pH range of 3 to 5. Absorption primarily occurs in the proximal small intestine with an absolute bioavailability of 62%. The volume of distribution is estimated to be 107 liters and plasma protein binding is estimated to be about 55% for concentrations from 0.2 to 5 ug/mL. Edoxaban metabolism is primarily mediated by carboxylesterase 1 (CES1) and CYP3A4. M4, an active circulating metabolite in plasma, is formed following CES1 metabolism and contributes to 10% of the total edoxaban systemic AUC.
Approximately 50% of the total clearance of unchanged edoxaban is through the kidneys with the remaining half appearing in feces and bile. After oral administration, the terminal elimination half-life is 10 to 14 hours. Edoxaban is a substrate for P-gp with its active metabolite, M4, a substrate for the influx transporter OATP1B1. In-vitro evidence suggests equivalent efflux transport from P-gp and BCRP.[51]

In the registration trial for use in VTE, study patients on concurrent P-gp inhibitors with body weight < 60 kg or moderate renal impairment received an edoxaban dose reduction to 30 mg daily with patients on CsA excluded from the study.[47] Edoxaban prolongs the prothrombin time in a concentration-dependent manner with a linear relationship between edoxaban and anti-FXa. The AUC of drug concentration is a predictor of therapeutic response when compared to warfarin across subjects with normal, mild, or moderate renal function.[61]

The interaction between edoxaban and CsA has been evaluated in healthy volunteers. Co-administration with CsA resulted in a 73% increase in edoxaban peak concentration and 72% increase in AUC.[62] Furthermore, the active circulating metabolite was observed to increase by greater than 7-fold for the both peak concentrations and AUC. In the population pharmacokinetic analysis of all VTE studies, no significant exposure-response for bleeding was observed in in patients on 30 mg daily, however the risk of recurrent VTE was modestly higher (1.77% vs. 1.57%) compared to patients on 60 mg.[63] The product label outlines 30 mg once daily dose of edoxaban for patients with creatinine clearances between 15 to 50 mL/min, body weight ≤ 60 kg, or those on certain P-gp inhibitors.[60]

4.5. Apixaban

Apixaban is indicated for the treatment and prevention of VTE and reducing the risk of stroke in atrial fibrillation.[64] Absorption occurs primarily in the upper gastrointestinal tract with a reduction in its absorption witnessed in more distal sites of the intestines.[65] Alterations in gastric acidity is not anticipated to produce significant changes since apixaban has no ionizable groups across physiological pH. Apixaban has an absolute bioavailability of approximately 50% and demonstrates dose-proportional
increases in AUC for oral doses up to 10 mg. Approximately 87% of drug is bound to protein while the distribution volume is low at 21 liters. Metabolism is predominately through CYP3A4 with a quarter of its metabolites appearing in urine and feces. Less than a third of apixaban is eliminated through renal excretion whereas the remaining fraction occurs through biliary and intestinal secretion into the feces.

Apixaban is a substrate for P-gp and BCRP with an estimated half-life of 12 hours. Using in-vitro permeability and transport assays with transfected cell monolayers, apixaban undergoes concentration and time-dependent transport via P-gp and BCRP with efflux ratios between 23-38 and 8-12, respectively.[66] In inhibition studies using Caco-2 bidirectional monolayers together with CsA, a non-specific inhibitor of P-gp and BCRP, the observed inhibition of apixaban efflux was 64%.[51] The efflux of apixaban is inhibited by 13% in comparison to verapamil, a strong and specific inhibitor of P-gp. As a result, although P-gp has a role in apixaban intestinal efflux, BCRP-dependent transport may predominate.

A concentration-dependent increase in anti-FXa activity is observed following single and multiple oral doses of apixaban. Intrinsic and extrinsic covariates that predicted apixaban total clearance are age, sex, race, renal function and co-administration of dual moderate and strong CYP3A4 and P-gp inhibitors.[67] Independent contributions from age, sex, race, and co-medications resulted in less than a 25% increase in apixaban exposures. Those with mild, moderate and severe renal dysfunction were found to have 17%, 34%, and 56% higher exposures, respectively.

Considering that close to one-third of the total systemic clearance of apixaban is due to renal elimination, decline in renal function is expected to largely affect the magnitude of exposure. Although intrinsic covariates such as age, sex, and race identified less than a quarter change in apixaban exposures, clinicians should be cognizant of additive effects when multiple factors are present. Declining renal function from CNI exposure may also be synergistic with previously mentioned factors and can potentially contribute to higher apixaban exposures. The PK of apixaban was evaluated in 12 healthy male volunteers together with CsA and tacrolimus. Following multiple-doses of CsA and tacrolimus, the AUC and $C_{\text{max}}$ of a
single 10 mg apixaban dose was observed to increase by 20% and 43% for CsA but decline by 22% and 13% for tacrolimus when compared to apixaban alone, respectively.[68] The contrasting effects of cyclosporine and tacrolimus on apixaban exposure noted in the study were unexpected, and the mechanism unclear. Based on safety analyses, elevated apixaban exposure and peak concentrations alone after co-administration with CsA is not anticipated to pose any clinically relevant bleeding events. In the case of tacrolimus, a 22% reduction in exposure may not result in loss of efficacy as witnessed in subjects with body weights > 120 kg. With a 25% decline in apixaban exposures due to extreme body weight, a third as many patients experienced a stroke or thromboembolic compared to warfarin observed from pivotal trials in atrial fibrillation.[69] Additionally, although within the lower bounds of apixaban exposures, tacrolimus co-administration is not expected to confer loss of efficacy at the indicated 2.5 mg twice-daily dose for VTE prophylaxis.[67] Although each factor is independent, the synergism from body weight being greater than 120 kg and tacrolimus use should warrant further clinical monitoring as the combination of both may compromise efficacy.

8. Conclusion

VTE is common in solid organ transplant recipients. The decision to choose DOAC over warfarin in this subset of patients is largely limited by the perceived risk of DDIs leading to bleeding or thrombotic concerns provoked by CNI maintenance immunosuppression therapy. DOACs have much less dose-response variability than warfarin, and accordingly do not require therapeutic monitoring, dose titration, or frequent dosage adjustments. This is an attractive option for transplant recipients requiring anticoagulation considering a large majority of individuals require lifelong chronic medications for immunosuppression and other comorbidities. Unfortunately, DOACs may be underutilized based on the DDI potential provoked by CNI use for maintenance immunosuppression. A visual is provided in figure 2 which summarizes the available evidence relevant to the pharmacokinetic changes that best emulates
that of CsA and tacrolimus. In the absence of a dedicated DDI study between a particular DOAC and CNI, clinicians can extrapolate the information presented for an inhibitor that shares the same inhibitory pathway with caution. Rather, educating patients to monitor for signs of bleeding or thrombosis is encouraged at present.

9. Expert Opinion

For the transplant recipient, DOAC selection is individualized and based on factors that may attenuate higher or lower anticoagulant exposure while on a CNI. It is estimated that the 5-year risk of chronic kidney disease after non-renal transplant ranges between 7 to 21%. Indeed renal function may decline over time as a result of CNI exposure, age, and pre-existing comorbidities. Since a considerable fraction of DOACs are cleared by the kidneys, renal function is an important consideration when selecting an anticoagulant for the transplant recipient. Furthermore, an important consideration is the site of drug interaction. For example, interactions with dabigatran etexilate occur primarily at the absorption level where P-gp efflux in the intestines predominates. The active drug, dabigatran, is then renally cleared without further interaction with P-gp in elimination organs (e.g. biliary ducts) or drug metabolizing enzymes. In comparison, direct FXa inhibitors may have interactions occurring at the absorption and elimination phase. This may further enhance exposure and increase the probability of a bleeding event during which metabolism or excretion is inhibited (e.g. CsA). Together with declining renal function, bleeding risks may increase when both the absorption and elimination pathways are inhibited. Although one factor alone may not enhance the safety risk, presence of renal dysfunction, CNI, additional P-gp or CYP3A4 inhibitors (e.g. antifungals or antibiotics) or other covariates (e.g. extremes in body weight) may contribute to a higher likelihood of bleeding. In the case of apixaban co-administered with tacrolimus, the reduction in apixaban exposure and peak concentration does not warrant efficacy concern. However, the likelihood of any compromise to efficacy is currently unknown for individuals with > 120 kg in body weight.
co-medicated with apixaban and tacrolimus. Interestingly, data from a large cohort of 91,330 Taiwanese patients found no significant risk of major bleeding in combined DOAC users with concurrent use of CsA.[71] Although the population of those using CsA together with DOACs was small at 0.62%, the risk of a major bleed was observed to be five-times greater in those taking apixaban compared to propensity-score matched controls.

Bleeding during CsA and rivaroxaban therapy have also been reported in small observational studies.[72,73] Although the number of patients included were small, both trough rivaroxaban concentration and anti-FXa activity were within the ranges considered therapeutic at their respective doses.[74] It should be noted that with each case, the reported creatinine clearances were far below the threshold value of 80 mL/min for which rivaroxaban is contraindicated in patients receiving dual P-gp and moderate CYP3A4 inhibitors. These results reflect several important implications for clinical practice where 1) dosage adjustments should be made to reflect renal function and CNI co-administration, 2) although the use of anti-FXa activity as a correlate to plasma drug levels is appropriate for FXa inhibitors, calibration specificity of anti-FXa activity for the FXa inhibitor (i.e. rivaroxaban, apixaban, or edoxaban) is critical to make an accurate determination and 3) lastly, the choice of tacrolimus for immunosuppression may be favorable compared to CsA. In a single-center retrospective cohort study in 37 thoracic transplant patients on concomitant DOAC and CNI therapy, bleeding rates were comparable to those without DDIs during DOAC therapy.[75] Tacrolimus was used in 73% of patients with 78% of the patients on rivaroxaban. The median creatinine clearance at the initiation of DOAC therapy was 59 mL/min. DOACs were used first-line as anticoagulation therapy for VTE in this report. Lung transplant recipients received rivaroxaban as the preferred DOAC if their creatinine clearances were above 30 mL/min, whereas apixaban was selected for those with creatinine clearances less than 30 mL/min. Those with identified DDIs- including roughly a quarter of those on CsA- were found to not have any statistically significant incidences in bleeding
compared to those without identified DDIs. These observational studies, although limited in the sample size, may demonstrate the role of DOACs in transplant recipients requiring anticoagulation.

Considering that most maintenance immunosuppressive regimens now contain tacrolimus, bleeding risks with DOACs may be less of a concern from DDIs. In the case of those requiring immunosuppression using CsA, which is a P-gp, BCRP, OATP and moderate CYP3A4 inhibitor, dabigatran etexilate may be appropriate based on its predominate P-gp transport in the gastrointestinal tract. This recommendation can be complicated considering that regulatory labeling for CsA recommend against use with dabigatran etexilate.[16,17] In addition, real-world limitations such as complex physiological changes, affordability, or insurance coverage may discourage the use of one DOAC over another.

As thrombosis research continues, development of safer and effective anticoagulants may offer a solution to DDI concerns. As an example, darexaban, a FXa inhibitor in clinical development demonstrated no relevant interactions in the presence of strong dual P-gp and CYP3A4 inducers suggesting a low potential of clinically relevant DDIs.[74] Unfortunately, further development of the compound was discontinued. In addition, small molecules targeting factors XII and XI are in development and may provide a safer alternative to potential bleeding risks encountered with current DOACs.[75] Future research applying pharmacometric and pharmacoepidemiological methods using rich data sources like the electronic medical record would be most useful in determining the pharmacokinetic-pharmacodynamic interaction within this subgroup.

Taken together, clinicians should consider the complex physiological changes that affect the absorption and elimination of drugs following transplantation to fully optimize anticoagulation therapy in recipients. Monitoring for renal function is essential in order to individualize anticoagulation therapy with DOACs. Monitoring of anti-FXa levels requires a drug specific assay, drug dosed to steady state, and a rigid attention to dose and draw time. There is no standardized dose adjustment based upon anti-FXa level and for these reasons the use of monitoring is discouraged. Dosage adjustments should follow the product
labeling with attention to renal function. Although limited, pharmacokinetic-pharmacodynamic and observational data suggest that the use of CNIs, specifically tacrolimus, together with DOACs is safe and effective.

Drug doses used for primary prophylaxis of VTE are less than those used for treatment of acute thrombosis or for secondary prophylaxis for a prior thrombotic event. The magnitude of any DDI will be accordingly less. Additional bleeding events attributable to prophylactic/low dose anticoagulation are low. For these reasons, patients with solid organ transplantation should have doses of thromboprophylactics guided by the general FDA approval label for all agents. In general, if there is concern for need of an invasive procedure or short term increased bleeding risk in an inpatient setting, the use of an injectable agent such as enoxaparin or unfractionated heparin is preferable to a DOAC without a readily available reversible agent.
References


*Drug interaction study demonstrating lack of clinical impact of tacrolimus on drug metabolizing enzymes and transporters.*


This review provides a comprehensive overview of the physiological changes in solid organ transplant recipients and its impact on drug pharmacokinetics.


**Drug interaction study demonstrating the time-dependent inhibition of P-glycoprotein of perpetrator drugs on the PK of dabigatran in healthy volunteers.**


Xarelto (Rivaroxaban) [Package Insert]. Janssen Pharmaceuticals, Inc., Titusville, NJ.


**Drug interaction study between rivaroxaban and perpetrator drugs that share the interaction profile of calcineurin inhibitors in healthy volunteers.**


Savaysa (Edoxaban) [Package Insert]. Daiichi Sankyo, Inc., Basking Ridge, NJ.


**Drug interaction study between cyclosporine on edoxaban PK in healthy volunteers.**


Eliquis (Apixaban) [Package Insert]. Bristol-Myers Squibb Company, Princeton, NJ.


**Healthy volunteer study of apixaban absorption PK in various regions of the gastrointestinal tract.**


**Drug interaction study between cyclosporine and tacrolimus on apixaban PK in healthy volunteers.**


Incidence of chronic renal failure following a non-renal organ transplant. The incidence of renal failure has important implications on the dosing and renal elimination of DOACs.


First large-scale pharmacoepidemiological study of drug interactions between DOACs co-administered with calcineurin inhibitors.


Observational study describing elevated rivaroxaban exposures in patients treated with cyclosporine.


Table 1. Summary changes to DOAC pharmacokinetics measured as changes in peak concentrations (Cmax) and exposure (AUC).

<table>
<thead>
<tr>
<th>Drug</th>
<th>In-vitro Transporter Affinity</th>
<th>Perpetrator</th>
<th>Victim / Perpetrator Regimen Studied</th>
<th>Effect of P-gp and/or CYP3A4 Inhibition</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Predominantly P-gp dependent transport</td>
<td>Verapamil</td>
<td>Single-dosed DE 150 mg 2 hours before + verapamil IR 120 mg BID</td>
<td>Cmax: ↑18% AUC: ↑12%</td>
<td>Do not use together with P-gp inhibitor if creatinine clearance is &lt; 50 mL/min. Labeling for both cyclosporine formulations suggest avoiding co-administration with dabigatran.</td>
<td>[16, 17, 51, 52, 53]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
<td>Single-dosed DE 150 mg 2 hours before + ritonavir 100 mg daily</td>
<td>Cmax: ↓ 27% AUC: ↓ 29%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Ritonavir</td>
<td>Single-dosed DE 150 mg + ritonavir 100 mg daily</td>
<td>Cmax: ↑13% AUC: ↑15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Equivalent P-gp &amp; BCRP transport</td>
<td>Fluconazole</td>
<td>Single-dose rivaroxaban 20 mg+ fluconazole 400 mg daily for 5 days</td>
<td>Cmax: ↑28% AUC: ↑42%</td>
<td>Do not use together with P-gp and strong CYP3A4 inhibitor if creatinine clearance &lt; 80 mL/min. No dedicated CsA or Tacrolimus DDI conducted. Fluconazole is a BCRP inhibitor. Erythromycin is a P-gp and moderate CYP3A4 inhibitor.</td>
<td>[51, 58]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Erythromycin</td>
<td>Single-dose rivaroxaban 10 mg +erythromycin 500 mg TID for 4 days</td>
<td>Cmax: ↑38% AUC: ↑34%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Equivalent P-gp &amp; BCRP transport</td>
<td>Cyclosporine</td>
<td>Single-dose edoxaban 60 mg + single-dose CsA 500 mg</td>
<td>Cmax: ↑ 74% AUC: ↑ 73%</td>
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</tr>
<tr>
<td>M4 (active metabolite)</td>
<td>Unknown</td>
<td>Cyclosporine</td>
<td>Single-dose apixaban 10 mg + CsA 100 mg daily for 3 days</td>
<td>Cmax: ↑ 8.7 fold AUC: ↑ 6.9 fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Preferential BCRP-dependent transport</td>
<td>Cyclosporine</td>
<td>Single-dose apixaban 10 mg + tacrolimus 5 mg daily for 3 days</td>
<td>Cmax: ↑ 43% AUC: ↑ 20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tacrolimus</td>
<td></td>
<td></td>
<td>No clinically meaningful impact on efficacy or safety with elevated exposure together with CsA; reduced exposure together with tacrolimus.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommended dose of 30 mg once-daily. Patients on CsA were excluded from pivotal VTE trial. CsA is an inhibitor of OATP1B1 uptake for M4 metabolite. [51, 62]

Figure 1. Physiological changes following solid organ transplantation that impact the pharmacokinetics (absorption, distribution, metabolism, and excretion) of drugs.

Absorption
- Reduced gastric emptying and motility
- Fluctuation in gastric pH
- Changes in gastrointestinal drug transporters

Metabolism
- Induction of drug metabolizing enzymes
- Increase in hepatic blood flow
- Altered expression of drug transporters

Distribution
- Increase in body weight
- Hypoalbuminemia
- Elevated alpha-1-acid glycoprotein

Excretion
- Alterations in bile flow and drainage
- Reduced renal function

The illustration is a derivative of “Arterial circulation”, “Arrow”, “Capsule”, and “Complete digestive apparatus” by Servier Medical Art (https://smart.servier.com/) under the Creative Commons License (CC BY 3.0).
Figure 2: Effect of cyclosporine, tacrolimus, or similar perpetrator drugs on the pharmacokinetics of DOACs.

Results from dedicated drug-drug interaction studies in healthy volunteers for dabigatran, rivaroxaban, edoxaban (and M4 metabolite), and apixaban. Reference values for the individual direct oral anticoagulant are for the AUC and $C_{\text{max}}$ parameters in the absence of the co-administered drugs. $C_{\text{max}}$, peak concentrations. AUC, area under the plasma concentration-time curve from time zero extrapolated to infinity. CI, confidence interval.