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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

64 **Article Highlights**

65 - The calcineurin inhibitors, cyclosporine and tacrolimus, are commonly used in maintenance

66   immunosuppression regimens to prevent graft rejection following solid organ transplant.

67   Cyclosporine may have a higher likelihood of inhibiting drug metabolizing enzymes and transporters

68   compared to tacrolimus.

69 - Direct oral anticoagulant (DOAC) clinical trials often excluded those on either cyclosporine or

70   tacrolimus.

71 - Identifying intrinsic and extrinsic variabilities in the pharmacokinetics-pharmacodynamics in solid

72   organ transplant recipients may balance the risks of bleeding while maintaining adequate

73   anticoagulation.

74 - The Cockcroft-Gault formula using ideal body weight is used for dosing adjustments for apixaban and

75   edoxaban while actual body weight is used to adjust dabigatran and rivaroxaban.

76 - While limited, pharmacokinetic-pharmacodynamic and outcomes evidence suggests safe and

77   effective use of DOACs together with calcineurin inhibitors.

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

79 - Direct oral anticoagulant use should be avoided in the immediate post-operative period and

80   considered only after there is stability of renal and hepatic function and when bleeding risk has

81   stabilized.

82 - Dose adjustment should not be made in the setting of acute thrombosis. After at least three months

83   of therapy, intrinsic and extrinsic factors may inform the use of switching to attenuated dose for

84   secondary thromboprophylaxis

85

86

87

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 regimens 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

111   particularly appealing for use in clinical care, specific guidance in transplant patients is lacking since this

112   population has been excluded from clinical trials of DOACs.

113   Calcineurin inhibitors block several drug transporters and metabolizing enzymes. Direct oral

114   anticoagulants are substrates of specific drug transporters and metabolic enzymes involved in the

115   absorption and elimination of drugs. Given the incidence of VTE following solid organ transplant and the

116   prevalent use of CNIs in maintenance immunosuppressive regimens, the use of DOACs together with CNIs

117   may result in a drug-drug interaction (DDI). These drug interactions are most impactful at treatment doses

118   for labeled indications of venous thromboembolic disease or atrial fibrillation, rather than the lower doses

119   used for primary prevention of venous thromboembolic disease.

120

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

122   **2.1. Tacrolimus**

123   Tacrolimus is a macrolide antibiotic isolated from *Streptomyces tsukubaensis*. Its mechanism

124   involves complexation with the immunophilin FK-binding protein which produces immunosuppression by

125   downstream inhibition of cytokine production and a loss of T-lymphocyte activation, proliferation, and

126   response. Tacrolimus is part of maintenance immunosuppression in over 80% of kidney, pancreas, liver,

127   intestine, heart, and lung transplant recipients and is indicated for the prophylaxis of organ rejection in

128   kidney, liver and heart transplant.[10,11] Following oral administration, tacrolimus is extensively

129   metabolized by cytochrome P450 (CYP) CYP3A4 and CYP3A5 and is a substrate for permeability

130   glycoprotein (P-gp). It is unclear whether tacrolimus has the potential to inhibit drug metabolizing

131   enzymes or efflux transporters in humans. While in-vitro and non-human in-vivo models have described

132   a possible inhibitory effect on CYP3A4 and P-gp,[12] the pharmacokinetic impact of tacrolimus and other

133   CYP3A and P-gp substrates in healthy volunteers is likely to be clinically irrelevant in patient

134   populations.[13,14]

135

2.2. Cyclosporine

Isolated from the fungal species *Tolypocladiumin flatum* 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]

160 Lastly, drug elimination may be altered due to higher hepatic blood flow, upregulation of drug

161 metabolizing enzymes, changes in bile flow, or decline in renal function.[35-40]

162

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

164 No formal studies have investigated the PK of DOAC therapy in solid organ transplant recipients.

165 Variability derived from intrinsic (altered protein binding, obesity, gastric motility) and extrinsic (DDI)

166 factors following transplantation may contribute to significant inter-recipient variability in the exposure

167 and the efficacy or safety response to DOACs. For the purposes of this review, extrinsic factors- mainly

168 those contributed from DDIs- will be discussed in detail. Drug metabolizing enzymes and transporters

169 play an important role in the disposition of drugs. The drug transporters, P-gp and BCRP, are commonly

170 expressed in the intestinal epithelia where their expression limits entry of therapeutic drugs.[41] In

171 excretory organs, drug transporters function to remove endogenous and xenobiotic compounds.

172 Therefore, efflux mechanisms can result in pharmacokinetic DDIs between CNI and DOACs during the

173 absorption or elimination phases. For CsA an interaction in the intestine can be considerable, since a large

174 magnitude of the delivered dose is in unbound form compared to delivery to the liver. In the intestines,

175 the inhibition of P-gp and BCRP by CsA was estimated using physiologically based pharmacokinetic

176 modeling to be up to 80% and 67%, respectively.[42] Moreover, up to 97% of intestinal CYP3A4 is inhibited

177 following a single oral dose. [42] In the intestines, P-gp, BCRP and CYP3A4 activity returns to maximal

178 activity within 4-6 hours after discontinuing CsA. Within the liver, P-gp, BCRP, and CYP3A4 enzyme activity

179 is estimated to be reduced by 4%, 2%, and 26%, respectively.[42] Tacrolimus has been shown to share

180 common inhibitory mechanisms as CsA with significantly less inhibition potential. For stabilized renal

181 transplant patients receiving tacrolimus, intestinal and hepatic CYP3A4 and P-gp activities are

182 insignificant. In contrast, the activity of intestinal CYP3A4 were starkly elevated in patients on CsA together

183 with significant reductions in intestinal and hepatic P-gp.[43] These findings enforce the differential

184 effects of CsA and tacrolimus on drug metabolizing enzymes and transporters for which a greater variation

185 in drug exposure is anticipated for drugs co-administered with CsA. Clinically, the magnitude of tacrolimus

186 inhibition on CYP3A4 and P-gp is expected to be minimal at therapeutic drug doses. [12,43]

187   It is important to keep in mind that although the magnitude of inhibition of transporters and

188 enzyme may appear large, differential expression along the length of the small intestine and lower

189 abundance of protein relative to the liver may minimize drug interaction potential.[44] In the case of the

190 DOACs, clinically relevant DDIs may result at the level of absorption (i.e. the intestines) or elimination (i.e.

191 renal or non-renal routes) when given together with CsA or tacrolimus. All DOACs are substrates of drug

192 efflux transporters and, with the exception of dabigatran, substrates for CYP3A4. Use of P-gp or CYP3A4

193 inhibitors, especially CsA or tacrolimus, were mostly excluded from pivotal trials in patients during the

194 clinical development of each DOAC.[45-48] While information related to the clinical relevance of the DDI

195 in patient populations is limited, available PK studies in healthy volunteers may provide insight in the

196 magnitude of change and its relationship to safety and efficacy. **Table 1** summarizes the extrinsic factors

197 relating to DDIs for DOACs and their respective exposure and peak concentration changes in the presence

198 of their substrate transporter and/or enzyme inhibitor. In the absence of a dedicated CsA or tacrolimus

199 study, we reference available substrate transporter and/or enzyme inhibitors that share the same

200 mechanistic pathways to provide insight to the magnitude of changes in the exposure and peak

201 concentrations.

202 **4.1. Dabigatran**

203   Dabigatran etexilate directly and reversibly inhibits thrombin, rather than reducing the

204 production of vitamin K dependent clotting factors.[49] Dabigatran etexilate is a prodrug that is orally

205 absorbed with an absolute bioavailability of approximately 3-7%. Conversion to the active moiety,

206 dabigatran, is independent of CYP isoenzymes and is formed following hydrolysis by carboxylesterases. It

207 is the prodrug that is a substrate of P-gp rather than the active moiety, which may account for its low

208 bioavailability and variable PK. In addition, changes in gastric pH and intestinal motility have also

209 contributed to the observed differences in PK following surgery.[50] The volume of distribution is

210 moderate at 60 liters with an in-vitro plasma protein binding of 35% across therapeutic concentrations.

211 Dabigatran, but not dabigatran etexilate, is detectable in systemic circulation following oral

212 administration. Dabigatran metabolism is minimal and it is not a substrate or inhibitor of CYP450 enzymes.

213 Renal clearance is the major route of dabigatran drug elimination representing 80% of the total clearance.

214 Following intravenous dosing, greater than 80% of the dose was recovered in the urine compared to only

215 7% after oral administration. The remaining 86% of orally dosed dabigatran was recovered in the feces

216 most likely due to incomplete absorption of DE. Dabigatran elimination half-life is 12-17 hours.

217 Dabigatran etexilate exhibits predominately P-gp dependent transport, demonstrated by in-vitro

218 inhibition studies using verapamil as a P-gp inhibitor.[51] In the presence of CsA, a P-gp and BCRP inhibitor,

219 greater than 80% of efflux was inhibited as observed using the same in-vitro Caco-2 permeability model.

220 These results implicate CsA as a potential perpetrator for clinical in-vivo drug interactions following co-

221 administration with dabigatran etexilate. To date, no dedicated in-vivo clinical studies have been

222 conducted evaluating the DDI between dabigatran etexilate co-administered with either CsA or

223 tacrolimus. P-gp inhibition may be time-dependent and influenced by the timing of a co-administered

224 perpetrator. Following multiple oral doses of verapamil in healthy volunteers, total dabigatran exposure

225 and peak concentration increased by 54% and 63% after a single-oral 150 mg dabigatran etexilate dose 1

226 hour after verapamil, respectively.[52] When dabigatran etexilate was given 2 hours prior to verapamil,

227 exposure and peak concentration increased by 18% and 12%, respectively. Considering the inhibition

228 activity of CsA in-vitro, results from co-administered verapamil alone may not satisfy the clinical relevance

229 of both P-gp and BCRP inhibition. Insightful results based on in-silico modeling using ritonavir, a dual P-gp

230 and BCRP inhibitor, have estimated exposure and peak concentration increases of approximately 25% and

231 16%, using a simulated 200 mg twice-daily regimen, respectively.[53]

9

232   Dabigatran transporter mediated DDIs are best assessed using data obtained in healthy

233   volunteers using the broad ATP-binding transporter and CYP3A4 inhibitor ritonavir.[54] Following

234   multiple-oral doses of ritonavir 100 mg daily, single-dose dabigatran exposure was increased by 15% when

235   administered simultaneously and reduced by 29% when dabigatran etexilate was administered 2 hours

236   prior to dosing ritonavir. These observations likely confirm the time-dependency of co-administered

237   perpetrator drugs on the PK profile of dabigatran. P-gp inhibition and renal dysfunction are both

238   independent factors that enhances the exposure of DE.

239   In patients receiving dabigatran etexilate for treatment and prevention of VTE, there is no dosage

240   adjustment or contraindication to P-gp inhibitors so long as patients have a creatinine clearance greater

241   than 50 mL/min.[55] These recommendations are intuitive considering the most important factor

242   influencing dabigatran exposure is renal clearance. Therefore, the use of dabigatran etexilate is

243   completely contraindicated in those with creatinine clearances less than 50 mL/min. Despite these results,

244   the U.S. labelling for CsA suggests avoiding co-administration with dabigatran etexilate altogether

245   regardless of renal function.[16,17] Drug-drug interactions involving dabigatran etexilate may be

246   restricted to only intestinal P-gp rather than other sites. In addition, BCRP and CYP3A4 liability is not a

247   general concern as witnessed from in-vitro permeability models and clinical DDI studies using the P-gp,

248   BCRP and CYP3A4 inhibitor, ritonavir. Based on these findings, dabigatran is a suitable choice in transplant

249   patients co-prescribed CsA or tacrolimus, so long as estimated creatinine clearance is > 50 ml/min. As the

250   risk of higher exposures and subsequent bleeding risk will be low in those with creatinine clearances

251   greater than 50 mL/min using a CNI, caution should be enforced especially during periods of fluctuating

252   physiology during the post-transplant period. A shorter acting parenteral anticoagulant should be

253   considered before dabigatran until renal function stabilizes and the bleeding risk has declined. In the

254   setting of acute VTE, the label outlines at least five days of treatment be with a parenteral agent (heparin

255   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

280 increased by 34% and 38% after a single-dose of rivaroxaban. Similarly, the AUC and Cmax are increased

281 by 42% and 28% following co-administration with the combined moderate CYP3A4 and BCRP inhibitor

282 fluconazole. These individual elevations in the AUC and peak concentrations alone do not warrant a

283 dosage change or contraindication as these values fall within the ranges observed of drug use in the

284 general patient population. Although one intrinsic or extrinsic factor alone does not preclude the use of

285 rivaroxaban, the presence of greater than one factor may present a complex drug-drug and drug-disease

286 interaction producing a clinically significant increase in rivaroxaban exposure. When accounting for renal

287 function, age, and DDI with erythromycin, increase in the AUC by 1.9, 2.4, and 2.6-fold were predicted in

288 younger patients with mild, moderate, or severe renal impairment while co-administered erythromycin,

289 respectively.[59] The impact from older age with erythromycin (55-65 years old) predicted a 2.5, 2.9 and

290 3-fold increase in the AUC in individuals with mild, moderate or severe renal impairment, respectively.

291 Although these results should not be extrapolated to those using CsA or tacrolimus, cautious monitoring

292 and careful clinical consideration for rivaroxaban use should be practiced especially in older patients with

293 reduced renal function.

294 **4.4. Edoxaban**

295 Edoxaban is a selective inhibitor of FXa indicated for the risk reduction of stroke and emboli in

296 non-valvular atrial fibrillation and treatment of VTE.[60] Like dabigatran but unlike the other FXa

297 inhibitors, edoxaban is labeled to be started after 5 to 10 days of parenteral anticoagulation in the

298 treatment of acute VTE. Edoxaban demonstrates pH-dependent solubility where optimal dissolution is

299 achieved in the pH range of 3 to 5. Absorption primarily occurs in the proximal small intestine with an

300 absolute bioavailability of 62%. The volume of distribution is estimated to be 107 liters and plasma protein

301 binding is estimated to be about 55% for concentrations from 0.2 to 5 ug/mL. Edoxaban metabolism is

302 primarily mediated by carboxylesterase 1 (CES1) and CYP3A4. M4, an active circulating metabolite in

303 plasma, is formed following CES1 metabolism and contributes to 10% of the total edoxaban systemic AUC.

304   Approximately 50% of the total clearance of unchanged edoxaban is through the kidneys with the

305   remaining half appearing in feces and bile. After oral administration, the terminal elimination half-life is

306   10 to 14 hours. Edoxaban is a substrate for P-gp with its active metabolite, M4, a substrate for the influx

307   transporter OATP1B1. In-vitro evidence suggests equivalent efflux transport from P-gp and BCRP.[51]

308   In the registration trial for use in VTE, study patients on concurrent P-gp inhibitors with body

309   weight $\leq$ 60 kg or moderate renal impairment received an edoxaban dose reduction to 30 mg daily with

310   patients on CsA excluded from the study.[47] Edoxaban prolongs the prothrombin time in a

311   concentration-dependent manner with a linear relationship between edoxaban and anti-FXa. The AUC of

312   drug concentration is a predictor of therapeutic response when compared to warfarin across subjects with

313   normal, mild, or moderate renal function.[61]

314   The interaction between edoxaban and CsA has been evaluated in healthy volunteers. Co-

315   administration with CsA resulted in a 73% increase in edoxaban peak concentration and 72% increase in

316   AUC.[62] Furthermore, the active circulating metabolite was observed to increase by greater than 7-fold

317   for the both peak concentrations and AUC. In the population pharmacokinetic analysis of all VTE studies,

318   no significant exposure-response for bleeding was observed in in patients on 30 mg daily, however the

319   risk of recurrent VTE was modestly higher (1.77% vs. 1.57%) compared to patients on 60 mg.[63] The

320   product label outlines 30 mg once daily dose of edoxaban for patients with creatinine clearances between

321   15 to 50 mL/min, body weight $\leq$ 60 kg, or those on certain P-gp inhibitors.[60]

322   **4.5. Apixaban**

323   Apixaban is indicated for the treatment and prevention of VTE and reducing the risk of stroke in

324   atrial fibrillation.[64] Absorption occurs primarily in the upper gastrointestinal tract with a reduction in its

325   absorption witnessed in more distal sites of the intestines.[65] Alterations in gastric acidity is not

326   anticipated to produce significant changes since apixaban has no ionizable groups across physiological pH.

327   Apixaban has an absolute bioavailability of approximately 50% and demonstrates dose-proportional

328 increases in AUC for oral doses up to 10 mg. Approximately 87% of drug is bound to protein while the

329 distribution volume is low at 21 liters. Metabolism is predominately through CYP3A4 with a quarter of its

330 metabolites appearing in urine and feces. Less than a third of apixaban is eliminated through renal

331 excretion whereas the remaining fraction occurs through biliary and intestinal secretion into the feces.

332 Apixaban is a substrate for P-gp and BCRP with an estimated half-life of 12 hours. Using in-vitro

333 permeability and transport assays with transfected cell monolayers, apixaban undergoes concentration

334 and time-dependent transport via P-gp and BCRP with efflux ratios between 23-38 and 8-12,

335 respectively.[66] In inhibition studies using Caco-2 bidirectional monolayers together with CsA, a non-

336 specific inhibitor of P-gp and BCRP, the observed inhibition of apixaban efflux was 64%.[51] The efflux of

337 apixaban is inhibited by 13% in comparison to verapamil, a strong and specific inhibitor of P-gp. As a result,

338 although P-gp has a role in apixaban intestinal efflux, BCRP-dependent transport may predominate.

339 A concentration-dependent increase in anti-FXa activity is observed following single and multiple

340 oral doses of apixaban. Intrinsic and extrinsic covariates that predicted apixaban total clearance are age,

341 sex, race, renal function and co-administration of dual moderate and strong CYP3A4 and P-gp

342 inhibitors.[67] Independent contributions from age, sex, race, and co-medications resulted in less than a

343 25% increase in apixaban exposures. Those with mild, moderate and severe renal dysfunction were found

344 to have 17%, 34%, and 56% higher exposures, respectively.

345 Considering that close to one-third of the total systemic clearance of apixaban is due to renal

346 elimination, decline in renal function is expected to largely affect the magnitude of exposure. Although

347 intrinsic covariates such as age, sex, and race identified less than a quarter change in apixaban exposures,

348 clinicians should be cognizant of additive effects when multiple factors are present. Declining renal

349 function from CNI exposure may also be synergistic with previously mentioned factors and can potentially

350 contribute to higher apixaban exposures. The PK of apixaban was evaluated in 12 healthy male volunteers

351 together with CsA and tacrolimus. Following multiple-doses of CsA and tacrolimus, the AUC and C_{max} of a

352   single 10 mg apixaban dose was observed to increase by 20% and 43% for CsA but decline by 22% and

353   13% for tacrolimus when compared to apixaban alone, respectively.[68] The contrasting effects of

354   cyclosporine and tacrolimus on apixaban exposure noted in the study were unexpected, and the

355   mechanism unclear. Based on safety analyses, elevated apixaban exposure and peak concentrations alone

356   after co-administration with CsA is not anticipated to pose any clinically relevant bleeding events. In the

357   case of tacrolimus, a 22% reduction in exposure may not result in loss of efficacy as witnessed in subjects

358   with body weights $\geq$ 120 kg. With a 25% decline in apixaban exposures due to extreme body weight, a

359   third as many patients experienced a stroke or thromboembolic compared to warfarin observed from

360   pivotal trials in atrial fibrillation.[69] Additionally, although within the lower bounds of apixaban

361   exposures, tacrolimus co-administration is not expected to confer loss of efficacy at the indicated 2.5 mg

362   twice-daily dose for VTE prophylaxis.[67] Although each factor is independent, the synergism from body

363   weight being greater than 120 kg and tacrolimus use should warrant further clinical monitoring as the

364   combination of both may compromise efficacy.

365

366   **8. Conclusion**

367   VTE is common in solid organ transplant recipients. The decision to choose DOAC over warfarin in

368   this subset of patients is largely limited by the perceived risk of DDIs leading to bleeding or thrombotic

369   concerns provoked by CNI maintenance immunosuppression therapy. DOACs have much less dose-

370   response variability than warfarin, and accordingly do not require therapeutic monitoring, dose titration,

371   or frequent dosage adjustments. This is an attractive option for transplant recipients requiring

372   anticoagulation considering a large majority of individuals require lifelong chronic medications for

373   immunosuppression and other comorbidities. Unfortunately, DOACs may be underutilized based on the

374   DDI potential provoked by CNI use for maintenance immunosuppression. A visual is provided in **figure 2**

375   which summarizes the available evidence relevant to the pharmacokinetic changes that best emulates

376 that of CsA and tacrolimus. In the absence of a dedicated DDI study between a particular DOAC and CNI,

377 clinicians can extrapolate the information presented for an inhibitor that shares the same inhibitory

378 pathway with caution. Rather, educating patients to monitor for signs of bleeding or thrombosis is

379 encouraged at present.

380

381 **9. Expert Opinion**

382   For the transplant recipient, DOAC selection is individualized and based on factors that may

383 attenuate higher or lower anticoagulant exposure while on a CNI. It is estimated that the 5-year risk of

384 chronic kidney disease after non-renal transplant ranges between 7 to 21%.[70] Indeed renal function

385 may decline overtime as a result of CNI exposure, age, and pre-existing comorbidities. Since a considerable

386 fraction of DOACs are cleared by the kidneys, renal function is an important consideration when selecting

387 an anticoagulant for the transplant recipient. Furthermore, an important consideration is the site of drug

388 interaction. For example, interactions with dabigatran etexilate occur primarily at the absorption level

389 where P-gp efflux in the intestines predominates. The active drug, dabigatran, is then renally cleared

390 without further interaction with P-gp in elimination organs (e.g. biliary ducts) or drug metabolizing

391 enzymes. In comparison, direct FXa inhibitors may have interactions occurring at the absorption and

392 elimination phase. This may further enhance exposure and increase the probability of a bleeding event

393 during which metabolism or excretion is inhibited (e.g. CsA). Together with declining renal function,

394 bleeding risks may increase when both the absorption and elimination pathways are inhibited. Although

395 one factor alone may not enhance the safety risk, presence of renal dysfunction, CNI, additional P-gp or

396 CYP3A4 inhibitors (e.g. antifungals or antibiotics) or other covariates (e.g. extremes in body weight) may

397 contribute to a higher likelihood of bleeding. In the case of apixaban co-administered with tacrolimus, the

398 reduction in apixaban exposure and peak concentration does not warrant efficacy concern. However, the

399 likelihood of any compromise to efficacy is currently unknown for individuals with $\geq$ 120 kg in body weight

400   co-medicated with apixaban and tacrolimus. Interestingly, data from a large cohort of 91,330 Taiwanese

401   patients found no significant risk of major bleeding in combined DOAC users with concurrent use of

402   CsA.[71] Although the population of those using CsA together with DOACs was small at 0.62%, the risk of

403   a major bleed was observed to be five-times greater in those taking apixaban compared to propensity-

404   score matched controls.

405   Bleeding during CsA and rivaroxaban therapy have also been reported in small observational

406   studies.[72,73] Although the number of patients included were small, both trough rivaroxaban

407   concentration and anti-FXa activity were within the ranges considered therapeutic at their respective

408   doses.[74] It should be noted that with each case, the reported creatinine clearances were far below the

409   threshold value of 80 mL/min for which rivaroxaban is contraindicated in patients receiving dual P-gp and

410   moderate CYP3A4 inhibitors. These results reflect several important implications for clinical practice

411   where 1) dosage adjustments should be made to reflect renal function and CNI co-administration, 2)

412   although the use of anti-FXa activity as a correlate to plasma drug levels is appropriate for FXa inhibitors,

413   calibration specificity of anti-FXa activity for the FXa inhibitor (i.e. rivaroxaban, apixaban, or edoxaban) is

414   critical to make an accurate determination and 3) lastly, the choice of tacrolimus for immunosuppression

415   may be favorable compared to CsA. In a single-center retrospective cohort study in 37 thoracic transplant

416   patients on concomitant DOAC and CNI therapy, bleeding rates were comparable to those without DDIs

417   during DOAC therapy.[75] Tacrolimus was used in 73% of patients with 78% of the patients on rivaroxaban.

418   The median creatinine clearance at the initiation of DOAC therapy was 59 mL/min. DOACs were used first-

419   line as anticoagulation therapy for VTE in this report. Lung transplant recipients received rivaroxaban as

420   the preferred DOAC if their creatinine clearances were above 30 mL/min, whereas apixaban was selected

421   for those with creatinine clearances less than 30 mL/min. Those with identified DDIs- including roughly a

422   quarter of those on CsA- were found to not have any statistically significant incidences in bleeding

423   compared to those without identified DDIs. These observational studies, although limited in the sample

424   size, may demonstrate the role of DOACs in transplant recipients requiring anticoagulation.

425   Considering that most maintenance immunosuppressive regimens now contain tacrolimus,

426   bleeding risks with DOACs may be less of a concern from DDIs. In the case of those requiring

427   immunosuppression using CsA, which is a P-gp, BCRP, OATP and moderate CYP3A4 inhibitor, dabigatran

428   etexilate may be appropriate based on its predominate P-gp transport in the gastrointestinal tract. This

429   recommendation can be complicated considering that regulatory labeling for CsA recommend against use

430   with dabigatran etexilate.[16,17] In addition, real-world limitations such as complex physiological

431   changes, affordability, or insurance coverage may discourage the use of one DOAC over another.

432   As thrombosis research continues, development of safer and effective anticoagulants may offer a

433   solution to DDI concerns. As an example, darexaban, a FXa inhibitor in clinical development demonstrated

434   no relevant interactions in the presence of strong dual P-gp and CYP3A4 inducers suggesting a low

435   potential of clinically relevant DDIs.[74] Unfortunately, further development of the compound was

436   discontinued. In addition, small molecules targeting factors XII and XI are in development and may provide

437   a safer alternative to potential bleeding risks encountered with current DOACs.[75] Future research

438   applying pharmacometric and pharmacoepidemiological methods using rich data sources like the

439   electronic medical record would be most useful in determining the pharmacokinetic-pharmacodynamic

440   interaction within this subgroup.

441   Taken together, clinicians should consider the complex physiological changes that affect the

442   absorption and elimination of drugs following transplantation to fully optimize anticoagulation therapy in

443   recipients. Monitoring for renal function is essential in order to individualize anticoagulation therapy with

444   DOACs. Monitoring of anti-FXa levels requires a drug specific assay, drug dosed to steady state, and a rigid

445   attention to dose and draw time. There is no standardized dose adjustment based upon anti-FXa level and

446   for these reasons the use of monitoring is discouraged. Dosage adjustments should follow the product

447 labeling with attention to renal function. Although limited, pharmacokinetic-pharmacodynamic and

448 observational data suggest that the use of CNIs, specifically tacrolimus, together with DOACs is safe and

449 effective.

450   Drug doses used for primary prophylaxis of VTE are less than those used for treatment of acute

451 thrombosis or for secondary prophylaxis for a prior thrombotic event. The magnitude of any DDI will be

452 accordingly less. Additional bleeding events attributable to prophylactic/low dose anticoagulation are low.

453 For these reasons, patients with solid organ transplantation should have doses of thromboprophylactics

454 guided by the general FDA approval label for all agents. In general, if there is concern for need of an

455 invasive procedure or short term increased bleeding risk in an inpatient setting, the use of an injectable

456 agent such as enoxaparin or unfractionated heparin is preferable to a DOAC without a readily available

457 reversible agent.

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471 **References**

472   *** of Interest**
473   **** of considerable interest**

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Table 1. Summary changes to DOAC pharmacokinetics measured as changes in peak concentrations (Cmax) and exposure (AUC).
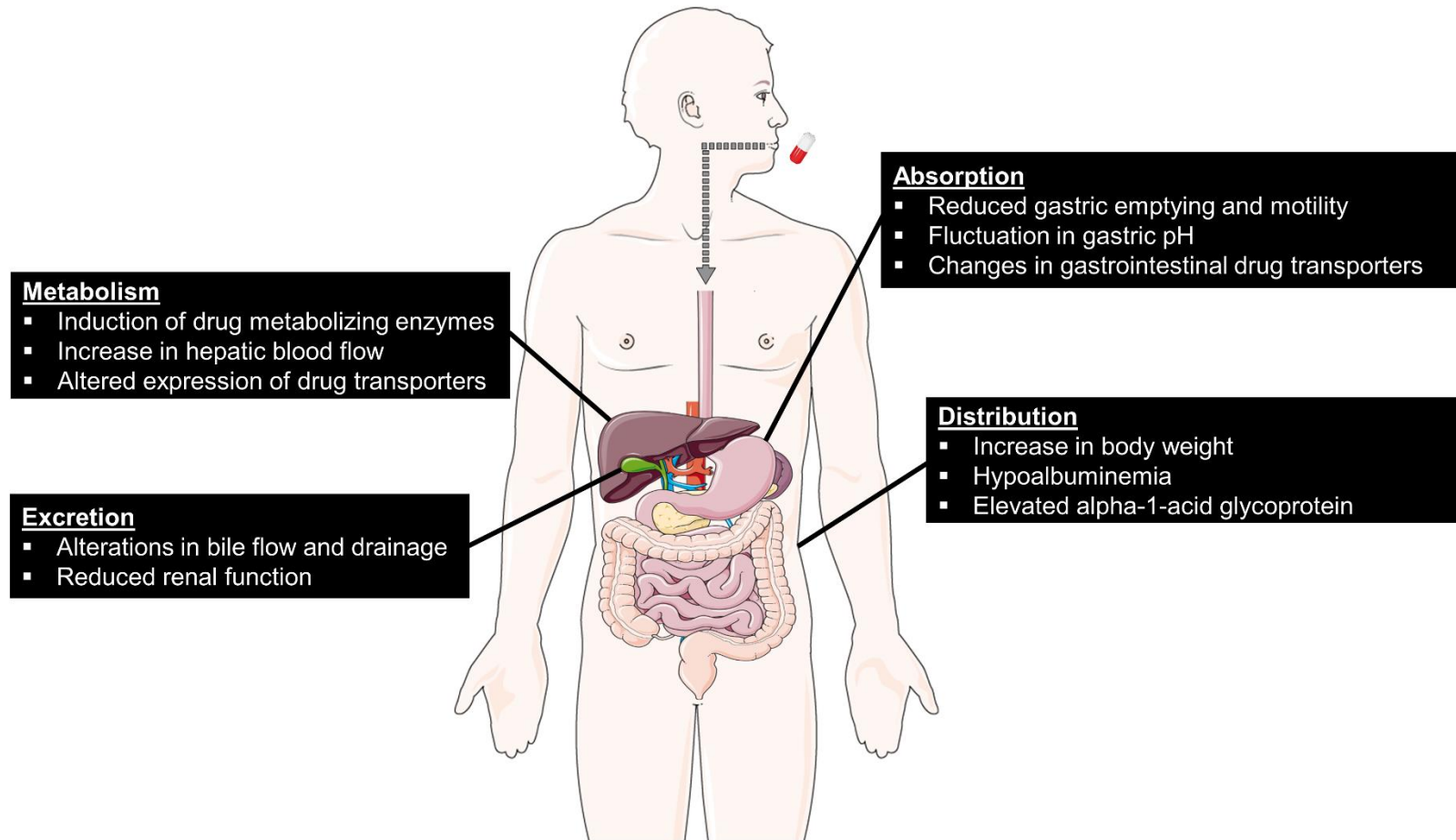
Drug	In-vitro Transporter Affinity	Perpetrator	Victim / Perpetrator Regimen Studied	Effect of P-gp and/or CYP3A4 Inhibition	Comments	Reference
Dabigatran	Predominantly P-gp dependent transport	Verapamil	Single-dosed DE 150 mg 2 hours before + verapamil IR 120 mg BID	Cmax: ↑18% AUC: ↑12%	Do not use together with P-gp inhibitor if creatinine clearance is < 50 mL/min. Labeling for both cyclosporine formulations suggest avoiding co-administration with dabigatran.	[16, 17, 51, 52, 53]
		Ritonavir	Single-dosed DE 150 mg 2 hours before + ritonavir 100 mg daily	Cmax: ↓ 27% AUC: ↓ 29%		
		Ritonavir	Single-dosed DE 150 mg + ritonavir 100 mg daily	Cmax: ↑13% AUC: ↑15%		
Rivaroxaban	Equivalent P-gp & BCRP transport	Fluconazole	Single-dose rivaroxaban 20 mg+ fluconazole 400 mg daily for 5 days	Cmax: ↑28% AUC: ↑42%	Do not use together with P-gp and strong CYP3A4 inhibitor if creatinine clearance < 80 mL/min. No dedicated CsA or Tacrolimus DDI conducted. Fluconazole is a BCRP inhibitor. Erythromycin is a P-gp and moderate CYP3A4 inhibitor.	[51, 58]
		Erythromycin	Single-dose rivaroxaban 10 mg +erythromycin 500 mg TID for 4 days	Cmax: ↑38% AUC: ↑34%		

Edoxaban	Equivalent P-gp & BCRP transport	Cyclosporine	Single-dose edoxaban 60 mg + single-dose CsA 500 mg	Cmax: ↑ 74% AUC: ↑ 73%	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]
M4 (active metabolite)	Unknown	Cyclosporine		Cmax: ↑ 8.7 fold AUC: ↑ 6.9 fold		
Apixaban	Preferential BCRP-dependent transport	Cyclosporine	Single-dose apixaban 10 mg + CsA 100 mg daily for 3 days	Cmax: ↑43% AUC: ↑20%	No clinically meaningful impact on efficacy or safety with elevated exposure together with CsA; reduced expsoure together with tacrolimus.	[51, 68]
		Tacrolimus	Single-dose apixaban 10 mg + tacrolimus 5 mg daily for 3 days	Cmax: ↓ 13% AUC: ↓ 22%		

687 AUC: Area under the plasma-concentration time curve extrapolated to infinity, BCRP: Breast Cancer Resistance Protein, BID: Twice-daily, C_{max}: Peak
688 plasma concentration, CsA: Cyclosporine, DDI: Drug-drug interaction, DE: Dabigatran etexilate, IR: Immediate-release, OATP: Organic anion
689 transporting polypeptide1B1, P-gp: Permeability glycoprotein, TID: Three times-daily
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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).

721 **Figure 2:** Effect of cyclosporine, tacrolimus, or similar perpetrator drugs on the pharmacokinetics of DOACs.
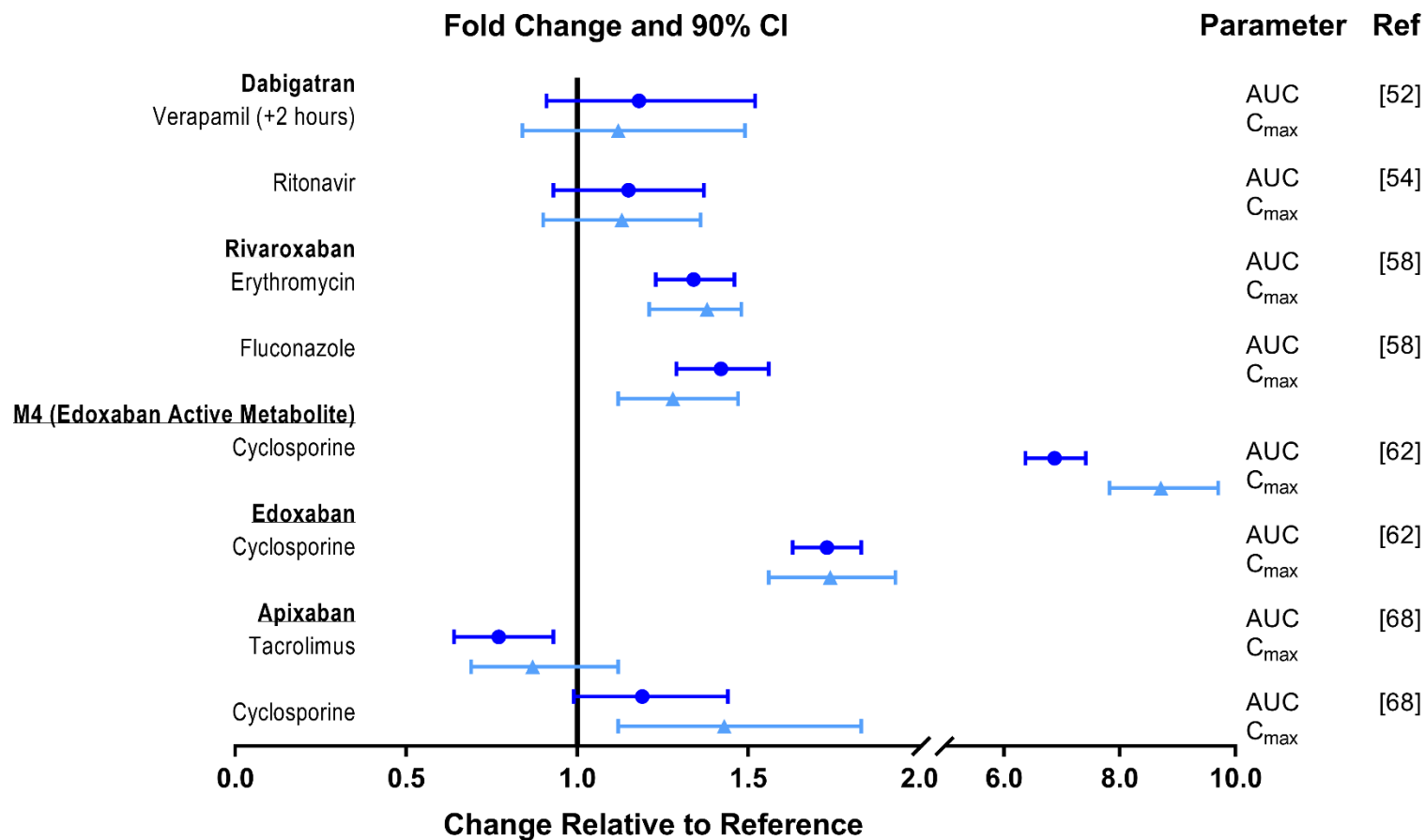
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739 Results from dedicated drug-drug interaction studies in healthy-volunteers for dabigatran, rivaroxaban, edoxaban (and M4 metabolite), and
740 apixaban. Reference values for the individual direct oral anticoagulant are for the AUC and C_{max} parameters in the absence of the co-administered
741 drugs. C_{max}, peak concentrations. AUC, area under the plasma concentration-time curve from time zero extrapolated to infinity. CI, confidence
742 interval.