Insights From Practice With Use of Direct Oral Anticoagulants in Transplantation

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Abstract
Solid organ transplant patients are at risk of developing atrial fibrillation and venous thromboembolism. Direct oral anticoagulants are considered an attractive option for anticoagulation in patients due to their convenience; however, strong evidence of their use in transplantation is lacking. We conducted a search using Pubmed, Embase, and Scopus databases, in addition to International Society of Heart and Lung transplantation and American Transplant Congress abstracts (from 2012 through December 2017). Fourteen articles were reviewed that included case reports, retrospective case series, or chart review analyses of small cohorts. Based on this review, the findings can only generate hypotheses that should be further studied in a larger randomized cohort. This review can help clinicians gain insight into the use of direct oral anticoagulant in this special population. For now, clinicians should be cautious about their use in this special population.

Keywords
direct oral anticoagulants, dabigatran, apixaban, rivaroxaban and transplantation

Introduction
Solid organ transplant patients are at risk of developing atrial fibrillation (Afib) and venous thromboembolism (VTE). Atrial fibrillation is a well-known risk factor for stroke and is associated with higher risk of morbidity and mortality.1 The cumulative incidence of Afib 3 years after transplant is 7.3% after kidney transplantation and ranges from 0.3% to 24% and 33% to 39% after heart and lung transplantation, respectively.2-4 The incidence of VTE is estimated to range from 2% to 34% based on the organ.5 The use of vitamin K antagonists for anticoagulation has several limitations, including narrow therapeutic index and drug-drug and drug-food interactions. Direct oral anticoagulants (DOACs) are considered an attractive option due to their convenient dosing and low potential for drug-drug interactions. The data about their use in this population are limited. Thus, we reviewed current published reports on real-world evidence of DOACs in transplant patients.

Dabigatran
The safety of dabigatran has not yet been determined. In a kidney transplant patient transplanted in the 1990s, a spontaneous perinephric hematoma was attributed to dabigatran (dose not reported) as the condition resolved after discontinuation of this drug in the absence of other risk factors.6 In a retrospective study of heart transplant patients (n = 23) on DOACs concomitantly with calcineurin inhibitors (CNIs), both tacrolimus and cyclosporine, patients on dabigatran were found to have a higher risk of developing major bleeds (P = .065) and more likely to have a decrease in tacrolimus dose (dose reduction not reported) during DOAC therapy compared to rivaroxaban or apixaban (P = .036).7 Time from transplant and DOAC dose were not reported.7

Literature Search Strategy
Our search used Pubmed, Embase, and Scopus databases and International Society of Heart and Lung transplantation and American Transplant Congress abstracts. The search included findings published between January 2012 and December 2017. Key words were dabigatran, rivaroxaban, apixaban, DOAC combined with transplantation. Fourteen articles are reviewed and summarized in Table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Purpose</th>
<th>Number of Patients</th>
<th>DOAC Used</th>
<th>Allograft Type</th>
<th>Authors’ Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Lisk et al</td>
<td>Case report</td>
<td>To describe a case of a simultaneous pancreas–kidney transplant recipient receiving dabigatran</td>
<td>1</td>
<td>Dabigatran</td>
<td>Pancreas–Kidney</td>
<td>• Organ transplantation, including pancreas, can be safely done on DOAC therapy.</td>
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<tr>
<td>Tralhao et al</td>
<td>Case report</td>
<td>To describe a case of reversal of the anticoagulant effect of dabigatran in a heart transplant patient</td>
<td>1</td>
<td>Dabigatran</td>
<td>Heart</td>
<td>• Idarucizumab seems to constitute a useful, rapidly acting, and effective dabigatran reversal agent in patients undergoing heart transplantation with recent drug exposure.</td>
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<tr>
<td>Rimsans et al</td>
<td>Case report</td>
<td>To describe a case of reversal of the anticoagulant effect of dabigatran in a heart transplant patient</td>
<td>1</td>
<td>Dabigatran</td>
<td>Heart</td>
<td>• Successful use of idarucizumab for a patient undergoing heart transplant surgery with no excess bleeding, requiring no blood product transfusions or concentrated clotting factor administration was reported.</td>
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<tr>
<td>Saxena et al</td>
<td>Case report</td>
<td>To describe a case of dabigatran-induced spontaneous perinephric hematoma in a kidney transplant recipient</td>
<td>1</td>
<td>Dabigatran</td>
<td>Kidney</td>
<td>• A spontaneous perinephric hematoma in a kidney transplant recipient on dabigatran in the setting of acute kidney injury was reported.</td>
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<tr>
<td>Zaleski et al</td>
<td>Case report</td>
<td>To describe a case of dabigatran-induced hyperkalemia in a renal-transplant patient.</td>
<td>1</td>
<td>Dabigatran</td>
<td>Kidney</td>
<td>• Dabigatran-induced hyperkalemia was reported in a kidney-transplant patient. Careful monitoring is recommended when prescribing dabigatran to patients with renal impairment.</td>
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<tr>
<td>Renner et al</td>
<td>Case report</td>
<td>To describe a case of a bilateral lung transplant patient receiving rivaroxaban</td>
<td>1</td>
<td>Rivaroxaban</td>
<td>Double lung</td>
<td>• A bilateral lung transplantation was safely done for a patient on rivaroxaban taking into account several factors including anti-Xa activity.</td>
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<td>Wannhoff et al</td>
<td>Case series</td>
<td>To investigate differences in rivaroxaban blood levels in liver transplant patients treated with CsA or Tac</td>
<td>9 all received a DOAC</td>
<td>Rivaroxaban</td>
<td>Liver</td>
<td>• The anti-Xa activity of rivaroxaban was significantly higher in patients taking CsA compared to those on tacrolimus ($P = .014$) even after accounting for differences in renal function and drug–drug interactions.</td>
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<tr>
<td>Wannhoff et al</td>
<td>Case series</td>
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<td>9 all received a DOAC</td>
<td>Rivaroxaban</td>
<td>Liver</td>
<td>• The authors suggest to only use rivaroxaban in liver transplant patients after thorough consideration and to monitor blood levels, especially with chronic kidney disease or receiving CsA.</td>
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<tr>
<td>Ambrosi et al</td>
<td>Case series</td>
<td>To describe heart transplant patients treated with rivaroxaban in a single center</td>
<td>11 all received a DOAC</td>
<td>Rivaroxaban</td>
<td>Heart</td>
<td>• Two cases of rivaroxaban overdosing was reported within the first 28 days of rivaroxaban initiation, mostly likely due to renal failure.</td>
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<td>• Rivaroxaban initiation should be discouraged in transplanted patients with a CrCl &lt; 30 mL/min.</td>
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<td>• A great caution is needed to use rivaroxaban that in transplanted patients with moderate renal failure (30 &lt; CrCl &lt; 60 mL/min).</td>
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</thead>
</table>
| Vanhove et al (2017) | Single-center Retrospective cohort analysis | To assess whether DOACs influence CNI exposure                         | 39                 | Rivaroxaban or Apixaban     | Kidney Lung Heart Kidney+ Lung | - Apixaban and rivaroxaban may cause a limited (<20%) increase in CNI trough concentration; however, it doesn’t seem to be clinically relevant as it did not trigger a dose change in CNIs.  
- An additional CNI trough concentration measurement 5 to 7 days after DOAC initiation may be prudent to perform but no need for preemptive CNI dose changes.  
- No statistical difference in rates of major bleeding between SOT recipients taking a DOAC versus warfarin concomitantly with a CNI ($P = .419$). |
| Hazelcorn et al (2017) | Single-center Retrospective chart review | To assess the incidence of major bleeding in SOT recipients taking CNI with a DOAC compared to patients taking warfarin | 77                 | Rivaroxaban or Apixaban     | Heart and other organs (not clearly mentioned) | - No statistical difference in rates of major bleeding between SOT recipients taking a DOAC versus warfarin concomitantly with a CNI ($P = .419$). |
| Lichvar et al (2016) | Single-center Retrospective cohort analysis | To describe a thoracic transplant patient population selected for DOAC therapy | 37                 | Dabigatran, Rivaroxaban or Apixaban | Heart Single lung Double lung | - DOAC therapy was well tolerated by thoracic transplant recipients.  
- No difference in the incidence of bleeding in patients with and without dug–drug interactions during DOAC therapy ($P = .154$).  
- No cases of DVT recurrence or strokes between the 2 groups. |
| Kim et al (2016) | Single-center Retrospective cohort analysis | To assess efficacy and safety of DOACs compared to traditional anticoagulants (LMWH, Fondaparinux or warfarin) in heart transplant recipients | 18                  | Dabigatran or Rivaroxaban   | Heart                           | - No difference in the incidence of bleeding between DOACs and traditional anticoagulants ($P = .39$). |
| Shuster et al (2016) | Single-center Retrospective cohort analysis | To determine the drug–drug interactions between DOACs and CNIs in heart transplant patients | 27                 | Dabigatran, Rivaroxaban or Apixaban | Heart                           | - There was a trend toward increased risk of major bleeds with dabigatran and CNI combination therapy when compared to A Xa and CNI use ($P = .065$).  
- A Xa inhibitor concurrent with CNI and diltiazem, possibly by CYP3A4 interaction, may increase the risks of bleeding in heart transplant patients compared to those not on diltiazem ($P = .039$). |
| Intagliata et al (2016) | Case report | To describe a case of reversal of the anticoagulant effect of dabigatran in a liver transplant patient | 1                  | Dabigatran and Apixaban     | Liver                           | - Successful use of idarucizumab for a patient undergoing liver transplant surgery with no excess bleeding, requiring no blood product transfusions, or concentrated clotting factor administration was reported. |

Abbreviations: DOAC, Direct oral anticoagulant; CNI, calcineurin inhibitors; LMWH, low molecular weight heparin; SOT, solid organ transplant; CsA, cyclosporine; Tac, tacrolimus.

*Last accessed December 2017.*
There were no case reports of dabigatran-induced bleeding in lung transplant recipients. Three case reports described successful idarucizumab use for reversal of dabigatran in patients undergoing heart and liver transplant surgeries. Patients did not experience a bleeding event that required blood transfusion in 2 reports. There were variations in dabigatran dose used. Kidney–pancreas transplant surgery was completed with dabigatran (dose not reported) without intraoperative bleeding that required blood transfusion.

Rivaroxaban

Rivaroxaban was found the most commonly used DOAC, mostly for heart transplant recipients. In a retrospective cohort analysis, heart transplant patients (n = 18) transplanted between January 2012 and June 2015, seven received DOACs: rivaroxaban, n = 5 (20 mg daily for Afib or atrial flutter; 15 mg twice daily then 20 mg daily for VTE; dabigatran, n = 1 (150 mg twice daily for atrial flutter); apixaban, n = 1 (2.5 mg twice daily for Afib); the rest received traditional anticoagulants. There was no bleeding episode reported with rivaroxaban and no cases of VTE recurrence or stroke.

Two cases of rivaroxaban overdose were observed among 11 heart transplant recipients on CNIs (8-28 years from transplant) within the first 28 days of receiving 15 mg once daily of rivaroxaban. The investigators measured trough anti-Xa activity and used the observed range in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study as a reference (12-137 ng/mL). All patients had trough anti-Xa activity of <137 ng/mL (56.0 (47.5) ng/mL) at day 14 of rivaroxaban use except 1 patient who had 137.4 ng/mL and CrCl of 25 mL/min. Another patient was admitted to the hospital for lower intestinal bleeding 8 days after rivaroxaban initiation, with CrCl of 25 mL/min and anti-Xa activity of 440 ng/mL 12 hours after last rivaroxaban dose. These overdose cases were attributed to renal impairment; however, the authors did not rule out a possible interaction between rivaroxaban and CNIs.

This interaction was studied in a retrospective analysis of 29 organ recipients in which rivaroxaban (dose not reported) caused 9.2% significant increase in tacrolimus trough concentration (n = 22; P = .042) and 12.7% increase in cyclosporine trough concentration (n = 7; P = .068) after correction for concomitant use of other CYP3A inhibitors. This increase was not clinically significant, as it was <20% and it did not trigger a CNI dose change.

In a case series of 9 liver transplant patients, rivaroxaban (dose not reported) trough anti-Xa activity (reference used 7-65 ng/mL) was significantly higher in patients treated with cyclosporine (n = 5) compared to those treated with tacrolimus (n = 4; 131 (119.5) vs 20.3 (14.4) ng/mL; P = .014, respectively) even after taking renal dose adjustments and drug–drug interactions into consideration. This increase in anti-Xa activity triggered a dose reduction in rivaroxaban by 5 mg in 3 cyclosporine-treated patients.

An increased risk of major bleeding was observed when heart transplant patients used rivaroxaban (dose not reported) concurrently with CNI and diltiazem compared to those who were not treated with diltiazem (P = .039); this may be attributed to CYP3A4 interaction.

A bilateral lung transplant was done with rivaroxaban (20 mg daily) using the guidance of anti-Xa activity. No blood transfusions were used during surgery (patient trough anti-Xa activity prior surgery was 36.9 ng/mL; reference used 9-147 ng/mL).

Apixaban

There were limited data about apixaban use. In a retrospective analysis (n = 39), 10 were on apixaban (dose not reported) and did not have a clinically significant effect on CNIs disposition, both cyclosporine (P = .156) and tacrolimus (P = .198).

All DOACs

In a single-center retrospective study that compared CNIs, mainly tacrolimus, with warfarin (n = 40) versus DOACs (n = 37; rivaroxaban and apixaban), no statistical difference was found in rates of major bleeding (P = .419).

In a retrospective analysis in thoracic transplant patients (n = 37; 80% lung), the majority used tacrolimus plus DOACs (dabigatran, rivaroxaban, and apixaban), and 8 bleeding events were reported with no difference in the incidence of bleeding in patients with and without drug–drug interactions during DOAC therapy (P = .154). There were no reported strokes or transient ischemic attacks.

Discussion

Direct oral anticoagulants are an attractive anticoagulation option because of standardized dosing and no required routine monitoring. However, little is known about their use in transplant patients who were excluded from landmark DOACs clinical trials. The available information was derived from real-world data by case reports, retrospective case series, or chart review analyses of small cohorts. Case reports may be flawed with selection bias. Retrospective case series or chart review analyses included small sample sizes and were not sufficiently powered to detect clinical differences between the groups. Therefore, current literature can only generate hypotheses and help clinicians gain insight into DOACs use in this special population.

Future research questions include the following: Can we safely perform a transplant on a patient who has been treated with a DOAC? What reversal options are available? What needs to be done during a biopsy? What are the efficacy and safety outcomes compared to traditional anticoagulants? Do DOACs interact with CNIs?

There are 4 case reports (2 in heart transplant, 1 in liver, 1 in pancreas–kidney) in which candidates were transplanted successfully on dabigatran. Dabigatran use may be appealing in transplant candidates because of the availability of the reversal
agent (idarucizumab); furthermore, it is the only DOAC that can be removed by hemodialysis. Reversal agents of Xa-inhibitors are not currently available; however, transplanting a patient on Xa-inhibitor can be done. Renner et al reported a successful bilateral lung transplantation in a patient on rivaroxaban without the need for a reversal agent or blood product; however, this transplant was performed under controlled conditions basing factors that included testing anti-Xa activity and the use of rotational thromboelastography. Currently, there is no information available about how to deal with DOACs during transplant biopsies.

Two small retrospective studies compared DOACs to traditional oral anticoagulants, mainly heart transplant patients, and found no significant difference in the incidence of bleeding between the 2 groups. There was no specific bleeding risk tool used, and until now there is no bleeding risk tool validated for transplant patients.

Both tacrolimus and cyclosporine are substrates for CYP 450 3A4 enzyme and P-glycoprotein (P-gp). Although only cyclosporine was proven to inhibit CYP 450 3A4 enzyme, both CNIs can inhibit P-gp. Among DOACs, only rivaroxaban and apixaban are metabolized by CYP 450 3A4 enzyme; however, all DOACs are substrates for P-gp, theoretically creating interactions between DOACs and CNIs. The current evidence suggests (1) dabigatran use concomitantly with CNIs may increase the risk of bleeding compared to rivaroxaban or apixaban, (2) rivaroxaban anti-Xa activity may be increased as it is used with CNIs, and (3) CNIs trough concentrations may be increased with rivaroxaban or apixaban. These hypotheses need to be tested in a larger cohort.

Whether starting a new transplant patient on a DOAC or continuing DOAC therapy after transplant, clinicians should consider several factors when making this decision. These factors include fluctuations in the renal function of transplanted patients, degree of coagulopathy, drug–drug interactions, the monitoring strategy of anticoagulation, and the reversal options for anticoagulation with DOACs.

Salerno et al reviewed DOACs use in patients with renal and hepatic impairment (no specific definitions described), considering drug–drug interactions with tacrolimus and cyclosporine and management of patients at the time of unplanned surgery. Based on the low-quality evidence, they recommended apixaban for patients with renal impairment. They did not recommend a specific DOAC for hepatic insufficiency for many reasons, but emphasized the importance of assessing the risk of bleeding before starting DOAC therapy. They also recommended discontinuing DOACs at the time of surgery and delaying use based on the medication half-life in any specific patient.

**Conclusion**

Making conclusive recommendations about DOACs use in solid organ transplantation are difficult because of the limitations of current literature. The available data have generated many hypotheses that should be further studied in a larger randomized cohort. For now, clinicians should be cautious about the use of DOACs in this population.

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**References**


