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REVIEW OF THERAPEUTICS

Use of direct-acting oral anticoagulants in solid organ transplantation: A systematic review

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Abstract

The use of direct-acting oral anticoagulants (DOACs) has increased secondary to the mounting evidence for comparable efficacy and potentially superior safety to vitamin K antagonists (VKAs) in the general population. However, insufficient data regarding DOAC use in solid organ transplant (SOT) recipients and numerous pharmacokinetic and pharmacodynamic considerations limit their use in this highly selected patient population. A systematic review of recent clinical evidence on the safety and efficacy of DOACs compared to VKAs in SOT recipients was conducted. Additional considerations including transplant-specific strategies for DOAC reversal and common pharmacokinetic/pharmacodynamic concerns were also reviewed. Although current evidence is limited to single-center retrospective analyses, DOACs, especially apixaban, appear to be a safe and effective alternative to VKAs for SOT recipients with stable graft function and without drug-drug interactions. Reliable data on DOAC reversal at the time of transplant surgery are lacking, and clinicians should consider idarucizumab, andexanet alfa, and other non-specific reversal agents on an individual patient basis. There is no evidence supporting deviations from the Food and Drug Administration labeling recommendations for DOAC dosing in the setting of drug-drug interactions, obesity, and renal function, especially in patients on hemodialysis.

KEYWORDS
apixaban, dabigatran, direct-acting anticoagulant, edoxaban, organ transplantation, rivaroxaban

1 | INTRODUCTION

Since the Food and Drug Administration (FDA) approval of dabigatran in 2010, direct-acting oral anticoagulants (DOACs) have been rapidly adopted for treatment of venous thromboembolism (VTE) and stroke prevention in non-valvular atrial fibrillation (NVAF).[1,2] Numerous studies have demonstrated comparable or superior efficacy of four DOACs in the aforementioned indications with a significantly lower risk of bleeding complications compared with warfarin.[3–10] While DOACs are the preferred anticoagulants over vitamin K antagonists (VKA) in the general population, the data examining safety and efficacy of DOACs in special patient populations are limited. In particular, solid organ transplant (SOT) recipients demonstrate unique pharmacokinetic considerations regarding renal and hepatic function as well as drug-drug interactions (DDIs).

Managing anticoagulation in patients receiving DOACs who are undergoing an unplanned transplant surgery or urgent allograft biopsy can also be challenging.[11] In more recent years, DOAC-specific reversal agents such as idarucizumab and andexanet alfa became available to manage life-threatening or uncontrolled bleeding from anticoagulation with DOACs.[12,13] Idarucizumab can also be considered to reverse the anticoagulant effect of dabigatran prior to emergency surgery and urgent procedures; however, safety and efficacy of other reversal strategies have not been well established for this indication.[14]

To provide insight into the practice trends of DOAC use in pre-, peri-, and post-transplant settings, a national survey was conducted among transplant pharmacists in the United States in 2019.[15] Of the 115 transplant programs responding to the survey, only 43 programs (37.4%) allowed DOACs in patients on the transplant waitlist. There were heterogeneous approaches to perioperative management of DOACs. While DOAC use was permissive in the post-transplant setting by 94.3% of the responding programs, patients' renal function and concomitant DDIs were among major factors that influenced prescribing decisions. Pharmacist perceptions on bleeding risk of DOACs in the SOT population were split between similar (38.3%) versus increased (33.0%) compared to the non-transplant population. The majority of survey respondents (64.3%) recognized that transplant-specific data on DOAC therapy are lacking.

To address the primary clinical questions identified from these survey results, this review will focus on: (a) whether DOACs are safer and/or more effective than VKAs in SOT recipients; (b) how DOACs should be reversed in the setting of SOT; and (c) how DOAC doses should be modified for special populations of SOT recipients.

2 | LITERATURE SEARCH AND REVIEW

In August 2020, a systematic search was conducted to identify studies evaluating the safety and efficacy of DOACs in adult (age >18 years old) SOT recipients including kidney, liver, pancreas, heart, and lung. PubMed was searched for English-language, full-text articles using the following combination of search terms: (DOAC OR "direct acting anticoagulant" OR "apixaban" OR "dabigatran"[MeSH] OR "edoxaban" OR "rivaroxaban"[MeSH]) AND ("Organ Transplantation"[MeSH] OR "Transplantation"[MeSH] OR "kidney transplant" OR "liver transplant" OR "lung transplant" OR "heart transplant"). Articles were excluded if the studies were not conducted in SOT recipients or did not evaluate safety or efficacy outcomes of DOAC. Additional studies were identified by reviewing references of relevant articles and searching abstracts presented at the American Transplant Congress (ATC) and the International Society for Heart & Lung Transplantation (ISHLT) between 2010 and 2020. Search terms for abstracts included: DOAC, direct acting anticoagulant, apixaban, dabigatran, edoxaban, and rivaroxaban. When evaluating the safety and efficacy of DOAC, preference was given to studies employing VKA as control. Eligibility assessment was performed independently by two reviewers. Disagreements were resolved by consensus. The following data were extracted from the included studies: study design, organ type, DOAC agents, bleeding complications, and thromboembolic events.

This study design followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16] All four investigators (AB, AL, DS, and JP) independently assessed and rated study quality following the Newcastle-Ottawa Scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for cohort studies.

For the DOAC reversal strategies and pharmacokinetic/pharmacodynamics considerations, references were qualitatively evaluated for relevance to peri-transplant settings. When transplant-specific evidence was lacking, data were supplemented from the general population. Based on the available literature, expert recommendations were formulated on criteria for appropriate use of DOAC reversal agents prior to transplant surgery and DOAC dosing in special patient populations.

3 | SAFETY AND EFFICACY OF DOAC IN SOLID ORGAN TRANSPLANT

A total of 120 publications were identified through the systematic search between January 1, 2010, and May 31, 2020. After applying the inclusion and exclusion criteria, nine English-language full-text articles were included in the content review (Figure 1). Seventeen abstracts reporting DOAC use in SOT recipients were identified from the meeting archives of ATC and ISHLT and were also summarized for discussion.

3.1 | Single-arm studies of DOACs

Prior to 2020, reports on the DOAC use among SOT recipients were limited to single-center, retrospective case series without control arms (Table 1).[17–42] Among the abstracts from ATC and ISHLT, the incidences of major bleeding (0%–23%) and composite bleeding (0%–37%) ranged widely, and the incidence of thrombotic events was also variable (0%–21%).

Five full-text articles described the safety and/or efficacy outcomes of DOACs in various SOT recipients in greater detail. The first study[21] was a case series of 11 heart transplant recipients taking rivaroxaban, of which one patient experienced severe bleeding. This patient had creatinine clearance (CrCl) of 25–30 ml/min, leading to the authors to conclude that rivaroxaban use should be discouraged in those with moderate renal impairment. Of the 42 kidney transplant recipients reviewed,[22] 7% experienced a major bleed. Apixaban was the most frequently prescribed DOAC (69%). Interestingly, 53% of patients received a DOAC dose reduction despite only 26.2% of patients being older than 75 years and an average estimated glomerular filtration rate (eGFR) of 62.9 ± 18.9 ml/min/1.73 m^2. Researchers[24] examined the interaction between calcineurin inhibitors (CNIs) and DOACs in 39 transplant recipients (kidney, lung, and heart). The authors reported 2 bleeding events during the average follow-up of 34 months. Other researchers[25] investigated the differences in rivaroxaban blood levels among nine liver transplant recipients on CNIs. Three of five patients on cyclosporine experienced a bleeding complication during a median follow-up of 11 months. The most robust single-arm study was a retrospective single-center cohort study of 37 thoracic transplant recipients.[23] Bleeding occurred in 19% of patients (major bleeding in 3%) during a median follow-up of 3 months. Based on a center-specific protocol, 60% of patients required a 50% DOAC dose reduction due to concomitant azole antifungal use.

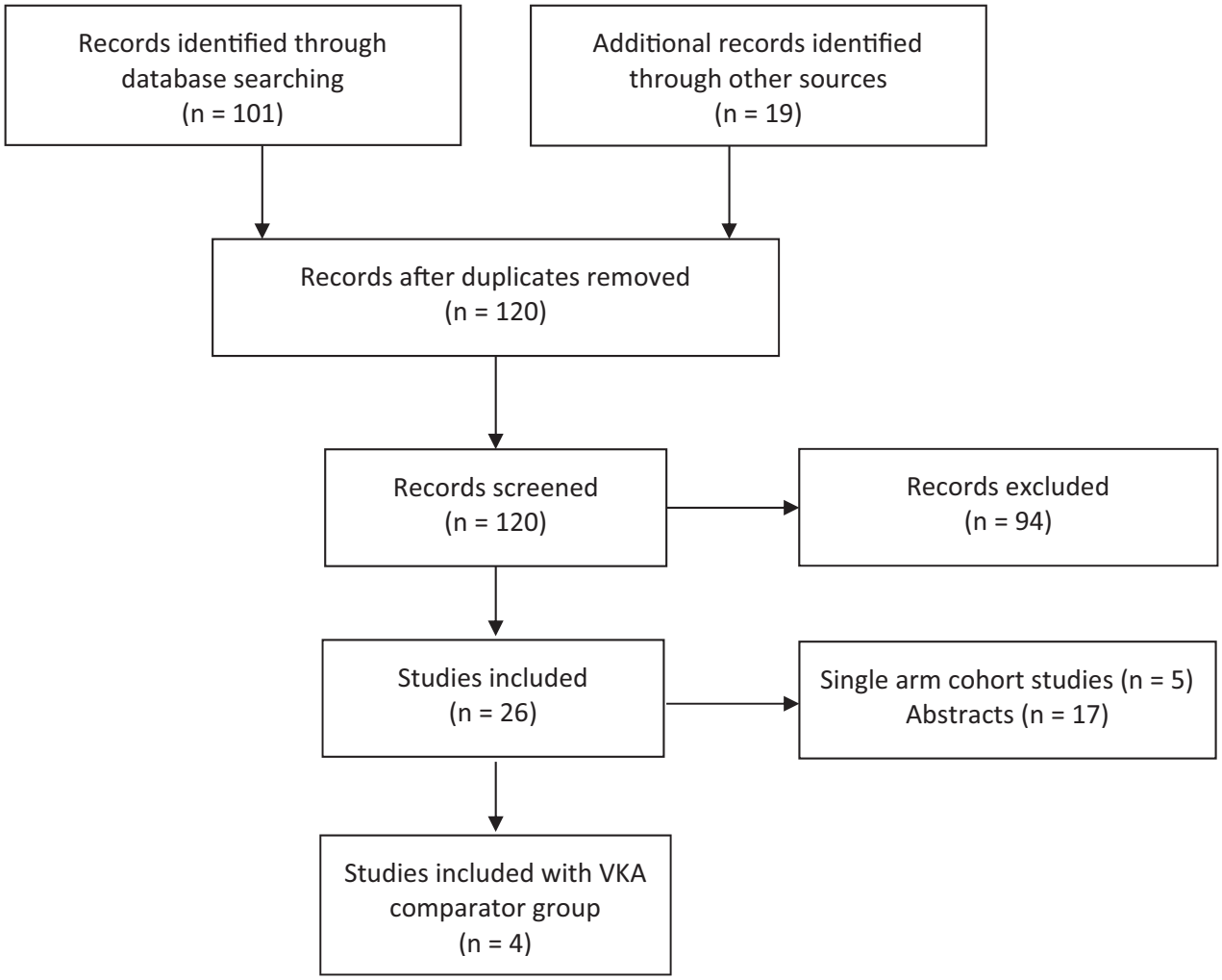

FIGURE 1 PRISMA flow diagram of studies included

Given the small sample sizes, heterogeneity in study designs, and lack of controls, conclusions could not be made from these single-arm cohort studies regarding the safety and efficacy of DOACs in SOT recipients.

3.2 | Comparative studies of DOACs to VKAs

In early 2020, four single-center retrospective cohort studies were published comparing DOACs to VKAs in SOT recipients.[17–20] Table 2 summarizes the study population, anticoagulants, and efficacy and safety outcomes of the studies.[17–20] The NOS quality assessments for each study were listed in Table S1.[17–20]

3.2.1 | Liver transplantation

Researchers[20] compared 27 liver transplant recipients on DOACs to 20 matched controls on warfarin from 2014 to 2018. Patients were excluded with active malignancy, those that stopped anticoagulation prior to 2 months for reasons other than bleeding or thrombosis, and those without appropriate laboratory follow-up. DOAC patients were matched with warfarin controls based on type of transplant, age, history of hepatocellular carcinoma, indication for anticoagulation, HAS-BLED score, timing of anticoagulation with regards to transplant, and duration of anticoagulation. The primary endpoint was the incidence of clinically relevant major or non-major bleeding, defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria for bleeding.

Apixaban was the most frequently prescribed DOAC (55.6%), followed by dabigatran (25.9%) and rivaroxaban (18.5%). There were no significant differences in baseline characteristics. Less patients in the DOAC group experienced a clinically relevant bleeding event (15% vs. 45%, p = 0.01) over a similar follow-up period (356 vs. 434 days, p = 0.23). No major bleeding events occurred in patients on DOACs and four major bleeding events occurred in the warfarin group (two requiring transfusion, one retroperitoneal bleed, and one acute subdural hematoma). There was no difference in the incidence of thrombotic events (20% vs. 15%, p = 0.67). Five patients received inappropriate DOAC dose reductions and one patient was prescribed a higher dose than recommended. However, all of the patients that experienced a bleeding event were on appropriate dosing. One patient that was on

TABLE 1 Studies analyzing DOAC use in solid organ transplant recipients

Study	*N* (for DOAC)	Organ	Major bleed (%)	Composite bleed (%)	Thrombotic event (%)
Full-text comparative studies					
Reference[a17]	99	Kidney	9%	24%	3%
Reference[18]	51	Heart	—	10%	4%
Reference[19]	52	Kidney	0%	13%	0%
Reference[a20]	27	Liver	0%	11%	15%
Full-text single-arm studies					
Reference[21]	11	Heart	10%	—	0%
Reference[22]	42	Kidney	2%	7%	0%
Reference[23]	37	Heart or lung	3%	19%	5%
Reference[24]	39	Any	0%	5%	—
Reference[25]	9	Liver	—	33%	0%
Abstracts					
Reference[26]	23	Heart	0%	0%	0%
Reference[a27]	99	Kidney	9%	24%	3%
Reference[28]	162	Any	3%	17%	4%
Reference[29]	52	Kidney	4%	12%	4%
Reference[30]	37	Any	11%	—	—
Reference[31]	7	Heart	0%	14%	0%
Reference[32]	33	Kidney	0%	12%	0%
Reference[33]	22	Kidney	0%	0%	5%
Reference[34]	172	Any	—	6%	1%
Reference[35]	109	Heart or lung	1%	14%	9%
Reference[36]	38	Heart or lung	0%	16%	21%
Reference[37]	77	Any	—	13%	6%
Reference[a38]	27	Liver	—	11%	15%
Reference[39]	62	Kidney	23%	37%	0%
Reference[40]	27	Heart	9%	—	—
Reference[41]	94	Any	—	19%	7%
Reference[42]	62	Heart	—	—	—

Abbreviation: DOAC, direct-acting oral anticoagulant.

[a]Published both in a full-text article and an abstract.

lower than recommended dose experienced a thrombotic event. When the authors performed a univariate analysis of this matched cohort, warfarin use and a baseline eGFR <30 ml/min or total bilirubin ≥3 mg/dl was associated with clinically relevant bleeding. The final multivariable logistic regression showed that warfarin use (odds ratio [OR] 6.9, 95% confidence interval [CI] 1.1–44.6) and baseline eGFR <30 ml/min (OR 10.4, 95% CI 1.3–81.3) were associated with higher odds of clinically relevant bleeding. Based on these results, the authors concluded that DOAC use appeared relatively safe compared with warfarin in liver transplant recipients.[20]

3.2.2 | Kidney transplantation

A study[19] compared kidney transplant recipients taking DOACs (*n* = 52) to a control group taking warfarin or fluindione (*n* = 50) between 2013 and 2018. Patients were excluded if eGFR <30 ml/min/1.73 m^2 or had a mechanical valve. The co-primary efficacy outcomes were arterial thromboembolic events and venous thromboembolic events. The primary safety outcome was any bleeding event. Major bleeding was defined using the ISTH definition. The only significant differences between baseline characteristics included a higher HAS-BLED score, a shorter time post-transplant, and a lower baseline hemoglobin in the warfarin group. Twenty-five patients (48%) were on reduced doses of DOAC.

Over a mean follow-up of 14 ± 13 months in the DOAC group versus 22 ± 20 months in the VKA group (p = 0.08), there was no difference in VTE (0% vs. 8%, p = 0.054). However, fewer patients in the DOAC group experienced a bleeding event (13% vs. 42%, p = 0.003; hazard ratio [HR] 0.39, 95% CI 0.19–0.85). None of the bleeding events in the DOAC group were considered major. Of the four patients that were on a strong cytochrome P450 (CYP) 3A4 and/or P-glycoprotein

TABLE 2 Summary of studies comparing DOAC to vitamin K antagonists in solid organ transplant recipients (single-center retrospective cohort studies)

Study (NOS study quality rating)	Study treatments	Outcomes	Baseline characteristics	Efficacy outcome results	Safety outcome results
Liver transplant					
Reference (NOS: S 3 stars, C 2 stars, and O 3 stars)[20]	DOAC (*n* = 20): apixaban, dabigatran, rivaroxaban Warfarin (*n* = 20)	Primary efficacy endpoint: thrombotic event Primary safety endpoint: incidence of clinically relevant major or non-major bleeding	DOAC vs. warfarin: Age 60.3 ± 11.3 vs. 59.4 ± 11.1 years (p = 0.79) NVAF 25% vs. 25% VTE 55% vs. 35% (p = 0.24) Time post-transplant 676 (IQR 39–4023) vs. 1916 (IQR 24–4786) days (p = 0.54) HAS-BLED score 2 (1.5–3) vs. 2 (1.5–2.5) (p = 1.00) $CHADS_2$ 1 (1–3) vs. 3 (2–3) (p = 0.40)	DOAC vs. warfarin: Thrombotic events 20% vs. 15% (p = 0.67)	DOAC vs. warfarin: clinically relevant bleeding 15% vs. 45% (p = 0.01)
Kidney transplant					
Reference (NOS: S 4 stars, C 1 stars, O 2 stars)[19]	DOAC (*n* = 99): apixaban (*n* = 60), dabigatran (*n* = 6), rivaroxaban (*n* = 33) Warfarin (*n* = 98)	Primary efficacy endpoint: new-onset stroke, new-onset stroke or recurrent VTE Primary safety endpoint: incidence of major bleeding	DOAC vs. Warfarin: Age 62.0 (IQR 56.5–70.3) vs. 62.3 (IQR 54.4–68.4) (p = 0.52) Time post-transplant 6.5 (IQR 2.8–10.8) vs. 6.4 (IQR 1.6–12.5) years (p = 0.98) NVAF 54% vs. 42% VTE 47% vs. 58% (p = 0.10) ATRIA 3.2 ± 1.9 vs. 3.6 ± 2.1 (p = 0.21) CHA_2DS_2-VASc 3.5 ± 1.7 vs. 3.5 ± 1.4 (p = 0.27)	DOAC vs. Warfarin: Stroke 1.0% vs. 5.1% (p = 0.13) VTE 2.0% vs. 3.1% (p = 0.50)	DOAC vs. Warfarin Major bleeding 9.1% vs. 21.4% (p = 0.15) Composite bleeding 24.2% vs. 34.7% (NS in time to event analysis)
Reference (NOS: S 3 stars, C 0 stars, O 3 stars)[17]	DOAC (*n* = 52): apixaban (*n* = 36), dabigatran (*n* = 1), rivaroxaban (*n* = 15) vs. VKA (*n* = 50): warfarin (*n* = 20), fluindione (*n* = 30)	Primary efficacy endpoint: arterial thromboembolism event or VTE event Primary safety endpoint: any bleeding	DOAC vs. VKA: Age 62 ± 13 vs. 60 ± 11 years (p = 0.45) Time post-transplant 87 ± 95 vs. 65 ± 90 months (p = 0.049) NVAF 60% vs. 42% (p = 0.11) VTE 29% vs. 44% (p = 0.15) HAS-BLED score 2.9 ± 1.3 vs. 2.4 ± 1.1 (p = 0.044) CHA_2DS_2-VASc 3.4 ± 1.7 vs. 3.2 ± 1.5 (p = 0.81)	DOAC vs. VKA: Arterial thromboembolism 0% vs. 0% (p = 1.0) VTE 0% vs. 8% (p = 0.054)	DOAC vs. VKA: Any bleeding event 13% vs. 42% (p = 0.002)
Heart transplant					
Reference (NOS: S 3 stars, C 1 stars, O 2 stars)[18]	DOAC (*n* = 51): apixaban (*n* = 35), dabigatran (*n* = 14), rivaroxaban (*n* = 2) Warfarin (*n* = 22)	Primary safety endpoint: any bleeding event requiring intervention	DOAC vs. Warfarin: Age: 58 (IQR 51–65) vs. 54 (IQR 46–62) (p = 0.28) Time post-transplant 42 vs. 75 days (p = 0.29) NVAF 13.7% vs. 13.6% VTE 84.3% vs. 77.3% (p = 0.60)	VTE 4% vs. 0%	DOAC vs. Warfarin Bleeding event 10% vs. 23% (p = 0.08)

Abbreviations: DOAC, direct-acting oral anticoagulant; IQR, interquartile range; NOS, Newcastle-Ottawa Scale; NVAF, non-valvular atrial fibrillation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

(P-gp) inhibitor or inducer, three patients experienced a bleeding event. Three of the 36 (8.3%) patients on apixaban and 4 of the 15 (26.7%) patients on rivaroxaban experienced a bleeding event. Characteristics of patients that experienced bleeding and severity of bleeding events were only reported for patients in the DOAC group (seven non-major bleeding events: one gastrointestinal, two urogenital, three subcutaneous hematoma, and one hemoptysis). The authors concluded that DOACs appeared to be effective and safe anticoagulants in kidney transplant recipients with stable graft function.[19]

Researchers[17] compared kidney transplant recipients taking DOACs (*n* = 99) to those taking warfarin (*n* = 98) between 2011 and 2018. Patients who required anticoagulation for mechanical valve, had inadequate follow-up, multiorgan transplant, gastrointestinal bleeding in the last 6 months, anticoagulation for <30 days (unless stopped early due to bleed), or indication for anticoagulation other than VTE and NVAF were excluded. The primary outcome was incidence of major bleeding defined using the ISTH definition. Baseline characteristics were similar with the exception of year anticoagulation started, antiplatelet use, and baseline hemoglobin. Reduced doses of DOACs were utilized in 19% of patients.

Over a median follow-up of 11.0 (interquartile range [IQR] 5.3–18.5) months in the DOAC group versus 13.1 (IQR 5.0–36.8) months in the warfarin group (p = 0.15), there was no difference in new-onset stroke (1.0% vs. 5.1%, p = 0.13) or VTE (2.0% vs. 3.1%, p = 0.50). Over the follow-up period, 9.1% of DOAC versus 21.4% of warfarin patients experienced a major bleed and 24.2% versus 34.7% experienced a composite bleeding event. When accounting for time, there was no statistical difference in major bleeding (Mantel-Cox p = 0.15) or composite bleeding. After multivariable Cox regression, DOAC use was not associated with an increased risk of bleeding (HR 0.73, 95% CI 0.27–1.95). When stratified by agent, there was a lower incidence of major bleeding with apixaban compared to all other anticoagulants (6.7% vs. 19.0%, p = 0.027). Similarly, there was a lower incidence of major bleeding when apixaban was compared with warfarin (6.7% vs. 21.4%, p = 0.014). The authors concluded that further research is warranted to definitively determine whether DOACs are safe and effective alternatives to warfarin for kidney transplant recipients.[17]

3.2.3 | Heart transplantation

Another study[18] evaluated heart transplant recipients taking a DOAC (*n* = 51) or warfarin (*n* = 22) between January 2012 and July 2019. Except for more patients in the warfarin group on dialysis (22.7% vs. 3.9%, p = 0.01), there were no significant differences in baseline characteristics. There was no difference in duration of follow-up between the groups (DOAC 130 days [IQR 84.5–203] vs. warfarin 93.5 days [IQR 59–183], p = 0.15). Two recurrent VTE events occurred in the DOAC group (one progressive upper extremity VTE and one fatal pulmonary embolism) and both patients were taking reduced dose apixaban due to concomitant itraconazole use. Bleeding occurred in 23% of warfarin patients and 10% of DOAC patients (p = 0.08). From both groups, there were three gastrointestinal bleeds, three intracranial bleeds, two abdominal hematomas, and two patients with epistaxis. In their Cox regression model, female sex was the only variable predictive of bleeding (HR 6.7, 95% CI 1.8–25.2). DOAC use was not associated with bleeding (HR 0.34, 95% CI 0.10–1.20). However, DOAC use was associated with a lower rate of bleeding requiring transfusion (p = 0.04). The authors of this study concluded that anticoagulation with a DOAC demonstrated a trend toward a lower rate of bleeding when compared to warfarin, but a larger cohort is needed to validate these findings.[18]

3.3 | Clinical implications

In this review, four studies were discussed comparing the safety and efficacy of DOACs to VKAs among SOT recipients.[17–20] There was no significant difference in efficacy with regard to VTE or stroke in any of the studies. Three of the four studies used the ISTH definitions to report bleeding outcomes. Consistently, all four studies found a numerically lower incidence of bleeding with DOACs than that with warfarin. Higher rates of bleeding were observed with both DOACs and warfarin in SOT recipients compared to the general population.[3–10]

Apixaban was the most commonly prescribed DOAC. which is consistent with the national survey of transplant center practices.[15] A study[18] did not find a significant difference in bleeding events between warfarin and apixaban in heart transplant recipients (p = 0.09). However, another study[17] found a lower incidence of major bleeding with apixaban compared to any other oral anticoagulants in kidney transplant recipients (p = 0.027). Similarly, a recent abstract comparing various DOACs in SOT recipients reported that apixaban was associated with less bleeding than dabigatran and rivaroxaban (12.5% vs. 33.3%, p = 0.017).[41]

Differences in dosing regimens may lead to differences in the bleeding incidence seen among different transplant centers. Researchers[20] reported that 18.5% of DOAC patients were on doses not compliant with the prescribing guidelines. Another group[19] reported that 48% of DOAC users were on reduced dose but did not report whether these dose adjustments were appropriate. It was reported[17] that 19% of DOAC patients were on a reduced dose and 13% of patients were inappropriately on a reduced dose of a DOAC. Although a group[18] did not report the number of patients requiring dose adjustments, they did describe that dose adjustments were made according to renal function, weight, age, and DDIs. Inconsistent practices in DOAC dose reduction is a major limitation of the current data. In the national survey of transplant centers, 51.5% of respondents answered that they follow the recommended dosing in the prescribing information.[15] Of those who deviated, 56.3% reduced the DOAC dose even with only one concomitant DDI. Until more consistent dose reduction criteria are utilized in transplant recipients, comparing bleeding rates between institutions will remain a challenge.

Additionally, combining patients taking anticoagulation for various indications is a limitation the present studies. However, researchers[17] included DOAC use for atrial fibrillation into their multivariable Cox regression and found that it did not increase risk for major bleeding (HR 2.11, 95% CI 0.94–4.11, p = 0.071). Based on the current data, DOACs, particularly apixaban, appear to be a safe and effective alternative to warfarin for transplant recipients with stable graft function and without DDIs.

4 | PERIPROCEDURAL MANAGEMENT AND REVERSAL OF DOAC THERAPY

The periprocedural management of DOACs and reversal strategies remain controversial and heterogeneous across the transplant landscape. In the recent survey of transplant programs, 37.4% of respondents allow patients to be maintained on DOAC therapy while they are on the transplant waitlist.[15] The varied nature of DOAC utilization during the pre-transplant period drives the need to understand the clinical management, monitoring, and reversal of DOACs in the setting of surgical procedures.

4.1 | Clinical monitoring of DOACs

Direct-acting oral anticoagulants have variable effects on coagulation assays, and there are different clinical implications of these effects (Table 3).[43,44] Despite the availability of laboratory assessments, only 29.4% of transplant centers report using routine laboratory monitoring to assess safety prior to transplant surgery in the setting of a DOAC therapy.[15] Limitations behind their limited use is delayed turnaround time, lack of individual agent calibration, and lack of quantitative measures that clinically relate to anticoagulation expectations and bleeding in the setting of surgery.

Dabigatran, a direct thrombin inhibitor, can alter activated partial thromboplastin time (aPTT), thrombin time (TT), dilute thrombin time (dTT), ecarin clotting time (ECT), prothrombin time (PT) and international normalized ratio (INR).[43] Out of these markers, dTT and ECT, and the plasma drug concentration itself are all thought to be sensitive markers that have some quantitative utility. The dTT is a coagulation test that measures coagulation by diluting plasma to better measure the activity of thrombin and has a linear dose relationship with dabigatran.[44] The dTT can indicate anticoagulation intensity, and in the setting of a normal value, is indicative of no clinically relevant anticoagulation effect from dabigatran. The ECT and plasma drug concentration, while sensitive, are infrequently available in clinical practice.

Factor Xa inhibitors can alter PT, aPTT (with the exception of apixaban), and anti–factor Xa levels.[43,44] The PT is not sensitive enough to exclude clinically relevant anticoagulation effect; furthermore, it is less sensitive to apixaban compared to edoxaban and rivaroxaban.[43] Secondly, aPTT is less sensitive than PT and does not have a role in factor Xa inhibitor clinical monitoring, as a normal aPTT

TABLE 3 Impact of DOACs on anticoagulation monitoring parameters[43,44]

Assay	Function	Sensitivity in direct thrombin inhibitors	Effect in direct thrombin inhibitors	Utility in direct thrombin inhibitors	Sensitivity in factor Xa inhibitors	Effect in factor Xa inhibitors	Utility in factor Xa inhibitors
Activated partial thromboplastin time (aPTT)	Activity and presence of FII, FV, and FIII/FXII	Not sensitive	Increased	Qualitative assessment, normal does not rule out effect	Low	Increased for all but apixaban	No utility in routine clinical practice
Anti-Xa	Concentration-dependent inhibition of FXa	–	–	–	High	Increased (trough dependent on FXa inhibitor)	Quantitative, if calibrated to specific anticoagulant
Dilute thrombin time (dTT)	Diluted plasma to make a more sensitive test than TT	Sensitive	Increased Trough >200 ng/ml dTT ≥65 s associated with bleeds	Quantitative assessment	–	–	–
Ecarin clotting time (ECT)	Measures thrombin generation	Sensitive	Increased Tough 3× the upper limit of normal associated with bleeds	Quantitative assessment	–	–	–

TABLE 4 Limited utility of anticoagulation monitoring parameters for DOAC monitoring[43,45]

	Exclude clinically relevant[a] drug levels		Measure on-therapy or above on-therapy levels	
DOAC	Suggested test	Interpretation	Suggested test	Interpretation
Dabigatran	TT aPTT	*Normal TT*: excludes clinically relevant[a] levels *Prolonged TT*: does not discriminate between clinically significant and insignificant levels *Normal aPTT*: usually excludes clinically relevant[a] levels if a sensitive reagent is used	aPTT	*Prolonged aPTT*: suggests that on-therapy or above on-therapy levels are present *Normal aPTT*: may not exclude on-therapy levels, particularly if a relatively insensitive aPTT reagent is used
Apixaban	UFH or LMWH anti-FXa	*Normal PT and aPTT*: do not exclude clinically relevant[a] levels *UFH or LMWH anti-FXa*: below the lower limit of quantitation probably excludes clinically relevant[a] levels	PT	*Prolonged PT*: suggests that on-therapy or above on-therapy levels are present *Normal PT*: may not exclude on-therapy or above on-therapy levels, particularly if a relatively insensitive PT reagent is used
Betrixaban, edoxaban, rivaroxaban	UFH or LMWH anti-FXa	*Normal PT and aPTT*: does not exclude clinically relevant[a] levels *UFH or LMWH anti-FXa*: below the lower limit of quantitation probably excludes clinically relevant[a] levels	PT	*Prolonged PT*: suggests that on-therapy or above on-therapy levels are present *Normal PT*: may not exclude on-therapy levels, particularly if a relatively insensitive PT reagent is used

Abbreviations: aPTT, activated partial thromboplastin time; DOAC, direct-acting oral anticoagulant; dTT, dilute thrombin time; ECA, ecarin chromogenic assay; ECT, ecarin clotting time; INR, international normalized ratio; PT, prothrombin time; TT, thrombin time.

[a]The term "clinically relevant" refers to DOAC levels that may contribute to bleeding or surgical bleeding risk. The minimum DOAC level that may contribute to bleeding or surgical bleeding risk is unknown. The International Society on Thrombosis and Hemostasis recommends consideration of anticoagulant reversal for patients with serious bleeding and a DOAC level >50 ng/ml, and for patients requiring an invasive procedure with high bleeding risk and a DOAC level >30 ng/ml.[106]

does not exclude on-therapy levels. After specific agent calibration, anti-factor Xa levels can be used for quantitative assessment and are the best monitoring parameter for this class of DOACs. Anti–factor Xa levels can be utilized to assess on-therapy or supratherapeutic levels if this calibration is performed (Table 4).[43,45]

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are visual assessments of clot formation, kinetics, and strength and have been assessed in the setting DOAC therapy.[46] With apixaban and dabigatran, the kaolin test reaction time (R time) and the time to maximum rate of thrombus generation were prolonged versus control samples. The utility of this laboratory monitoring parameter rests in its ability to guide intraoperative transfusion in the transplant surgery setting.[47]

4.2 | Periprocedural management of DOACs

Transplant surgery and allograft biopsies are generally categorized as high bleed risk procedures that require specific management in the setting of DOAC therapy.[14] In the setting of living donor transplantation or scheduled allograft biopsy, holding DOAC therapy is the most realistic and feasible clinical choice. The American College of Cardiology recommendations stratify duration of DOAC interruption based on the bleeding risk of the procedure and also CrCl as many DOACs have some degree of renal elimination (Table 5).[14,45]

Furthermore, the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study analyzed 3007 patients with atrial fibrillation on apixaban, dabigatran, and rivaroxaban.[48] In this particular assessment, perioperative DOAC interruption strategy was based on procedure-related bleeding risk and also CrCl. The 30-day postoperative rate of major bleeding was 1.35% (95% CI, 0%–2.00%) in the apixaban cohort, 0.90% (95% CI, 0%–1.73%) in the dabigatran cohort, and 1.85% (95% CI, 0%–2.65%) in the rivaroxaban cohort.[48] This study demonstrates that procedural pauses in DOAC therapy can result in low incidences of bleeding in the setting of elective procedures.

4.3 | Reversal of DOAC therapy

A major limitation to widespread DOAC utilization was a lack of specific reversal therapy, although specific agents are now available in the United States. In the recent survey, only 7.8% of transplant programs reported routine DOAC reversal at the time of transplant surgery, and of those programs using DOAC reversal, idarucizumab was most common for dabigatran reversal and 4-factor prothrombin complex concentrate (4F-PCC) for oral factor Xa inhibitors.[15]

Non-specific DOAC reversal agents can be used but are sometimes impractical in the setting of unexpected procedures and are used more so in the setting of acute ingestion or overdose. These modalities include activated charcoal, high-flow hemodialysis

TABLE 5 Recommendations for Pre-procedural Interruption of DOAC therapy (adapted from the 2017 ACC Expert Consensus Discussion Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation and the 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants)[14,45]

	Rivaroxaban (R), edoxaban (E), apixaban (A), betrixaban (B)			Dabigatran		
	$t_{1/2}$ (h)	Low risk	Uncertain, intermediate or high risk	$t_{1/2}$ (h)	Low risk	Uncertain, intermediate or high risk
CrCl ≥80 ml/min	6–15 (R, E, A) 19–27 (B)	≥24 h	≥48 h	13	≥24 h	≥48 h
CrCl 50–79 ml/min	6–15 (R, E, A) 19–27 (B)	≥24 h	≥48 h	15	≥36 h	≥72 h
CrCl 30–49 ml/min	6–15 (R, E, A) 19–27 (B)	≥24 h	≥48 h	18	≥48 h	≥96 h
CrCl 15–29 ml/min	R: 9 E: 17 A: 17	≥36 h	Not indicated. No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥72 h	27	≥72 h	≥120 h
CrCl <15 ml/min	R: 13 (ff dialysis) E: 10–17 (off dialysis) A: 17	Not indicated. No data. Consider measuring agent-specific anti-Xa level and/or withholding ≥72 h		30 (off dialysis)	Not indicated. No data. Consider measuring dTT and/or withholding ≥96 h (low risk procedures only)	

Abbreviations: CrCl, creatinine clearance; DOAC, direct-acting oral anticoagulant.

modalities, and plasmapheresis.[49] Both 4F-PCC and activated prothrombin complex concentrate (aPCC) can also be used off-label for DOAC reversal, despite not being specific reversal therapy agents.

4.3.1 | Reversal of direct thrombin inhibitor (dabigatran)

Dabigatran reversal is routinely performed with idarucizumab in clinical practice. Idarucizumab is a human monoclonal antibody fragment that binds to dabigatran and its metabolites, neutralizing their anticoagulation effect (Table 6).[50–53] In the RE-VERSE AD trial, 213 patients were analyzed and 68% had cessation of bleeding within 24 h with a median time to hemostasis of 2.5 h.[12] A subanalysis of surgical patients demonstrated that complete reversal of dabigatran effect occurred rapidly in 91% of the cohort, with a median time of drug administration to surgery to be 2 h in almost all groups.[54]

The use of idarucizumab in the setting of transplant recipients has limited data including case reports and small cohort experiences. There have been several case reports using this reversal modality in the setting of transplant surgery with success.[55–61] In a series of 10 patients receiving idarucizumab in the setting of heart transplantation, two patients (20%) required re-intervention because of bleeding which was similar to a historical control group.[60] In a multicenter observational study using idarucizumab reversal for 53 heart transplant recipients, 7.5% required re-operation in the immediate postoperative period to control bleeding, 66% required blood product transfusion, and 92.4% demonstrated 30-day survival.[59] One patient had surgical problems with right ventricular failure resulting in a death, which was the only mortality associated with bleeding. In the setting of inadequate reversal and suboptimal hemostasis, there have been reports of repeat idarucizumab dosing.[62] Per the prescribing information, in the setting of clinically relevant bleeding together with elevated coagulation parameters, then an additional dose of idarucizumab 5 g may be considered.[52]

In a prospective cohort study assessing the effect of aPCC for dabigatran reversal in the setting of major bleeding, hemostasis was determined to be "good" in 9 (64%), "moderate" in 5 (36%) and "poor" in none with no thrombotic events.[63] However, there are no data for this reversal strategy in the setting of urgent surgery in the absence of bleeding, and much of this use is extrapolated from data of in vitro, animal, healthy volunteer, and bleeding patients.[64] Likewise, there is no peer-reviewed published data for this agent in a transplant population.

Currently, guidance from the Anticoagulation Forum and 2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants recommends using idarucizumab 5 g intravenous (IV) for first-line dabigatran reversal with aPCC 50 units/kg IV as an alternative therapy.[45,64] Based on currently available literature, in the setting of the need for DOAC reversal in transplant recipients, idarucizumab should be first-line with aPCC as a secondary substitute for reversal. At this time, there are no specific data to guide whether repeat dosing is more effective than dosing aPCC, but given the achievement of hemostasis with primary idarucizumab dosing, this should be used before aPCC if there is enough supply to accommodate additional doses.

TABLE 6 Specific and non-specific DOAC reversal agents

	KCentra® (4 factor prothrombin complex concentrate, 4F-PCC)[50]	FEIBA® (anti-inhibitor coagulant complex, aPCC)[51]	Praxbind® (idarucizumab)[52]	Andexxa® (andexanet alfa)[53]
Classification	Non-specific prohemostatic agent		Specific antidote (humanized monoclonal antibody fragment)	Specific antidote (recombinant variant of human factor Xa)
Mechanism of action	II, VII, IX, X, Proteins C and S, heparin	II, VIIa, IX, X, VIII inhibitor bypassing activity	Binding to dabigatran and its metabolites neutralizing the anticoagulation effect	Binds oral factor Xa inhibitors and binds/inhibits tissue factor pathway inhibitor
Half-life ($t_{1/2}$)	Dependent on half-lives of individual clotting factors Elevated levels of clotting factors persistent for ~24 h		Pharmacodynamic: 45 min Terminal: 4–8 h	Pharmacodynamic: 30–60 min (anti-Xa rebound) Terminal: 5–7 h
Elimination	Hepatic		Renal	Unknown
Dose	Potency based on FIX content 2000 units × 1 dose (fixed dose) Alternative: 50 units/kg × 1 dose	Potency based on FVIII inhibitor bypassing activity in units 50 units/kg × 1 dose	2.5 g IV over 5 min × 2 doses	High dose bolus + infusion: 800 mg at 30 mg/min then 8 mg/min for up to 120 min Low dose bolus + infusion: 400 mg at 30 mg/min then 4 mg/min for up to 120 min
Onset	15 min (warfarin data)	15 min (warfarin data)	<5 mon	2–5 min

4.3.2 | Reversal of oral factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban)

The approach to oral factor Xa reversal is more heterogeneous compared to dabigatran. Specific reversal can be utilized with andexanet alfa, a recombinant variant of human factor Xa that binds to oral factor Xa inhibitors and inhibits the activity of tissue factor pathway inhibitor (Table 6). The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) Study analyzed 254 patients (100 on rivaroxaban, 134 on apixaban, 16 on edoxaban, and 4 on enoxaparin) and 352 for safety outcomes (128 on rivaroxaban, 194 on apixaban, 20 on edoxaban, and 3 on enoxaparin).[13] There was a 92% reduction in anti–factor Xa activity after the andexanet alfa bolus with excellent or good hemostasis occurring in 82% of patients on apixaban and 80% of rivaroxaban treated patients. A total of 14% died and 10% had thrombotic events within 30 days. Currently, no data exist for the use of andexanet alfa in the setting of urgent surgical procedural reversal or in the setting of transplant recipients.

Another option for DOAC reversal is 4F-PCC. In a study,[65] 84 patients received 4F-PCCs to reverse major bleeds from rivaroxaban and apixaban. Patients weighing <65 kg received 1500 units, and those weighing >65 kg received 2000 units. A total of 69% of patients achieved hemostasis. Furthermore, a prospective cohort study in Canada analyzed 66 patients who presented with major bleeds on rivaroxaban and apixaban and received 4F-PCC reversal.[66] In total hemostasis was categorized as "good" in 65%, "moderate" in 20%, and "poor" in 15%. In post-hoc analysis, reversal was effective in 68% of patients according to the ISTH criteria. A total of 8% of patients had thrombotic events within 30 days of their bleed reversal. The utilization of PCCs at the time of transplant surgery is limited to case reports.[67]

Guidance from the Anticoagulation Forum and 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants recommends using andexanet alfa for first-line oral factor Xa reversal with 4F-PCC utilization (2000 units fixed dose) as an alternative therapy.[45,64] Utilization of andexanet alfa in the setting of transplant reversal should be carefully considered and perhaps avoided based on the current paucity of literature and potential thrombosis risk. Figure 2 illustrates an overview of DOAC reversal in the setting of bleeding and urgent procedures.

5 | TRANSPLANT-SPECIFIC CONSIDERATIONS FOR DOAC USE

Pharmacokinetic/pharmacodynamic properties of individual DOAC agents that are pertinent to the SOT population have been examined in a previous comprehensive review.[11] Since the publication, there have been significant additions to the literature with regard to DDIs with common transplant medications, concomitant use with antiplatelet agents, and pharmacokinetics of DOACs in other specialized populations including obesity and hemodialysis. Approaches to DOAC dosing in these specific conditions will be discussed here.

5.1 | Drug interactions between DOACs and calcineurin inhibitors

Cyclosporine and tacrolimus are known substrates of CYP3A4 and P-gp. Both are inhibitors of P-gp, and cyclosporine is a moderate inhibitor of CYP3A4.[68] Both rivaroxaban and apixaban undergo

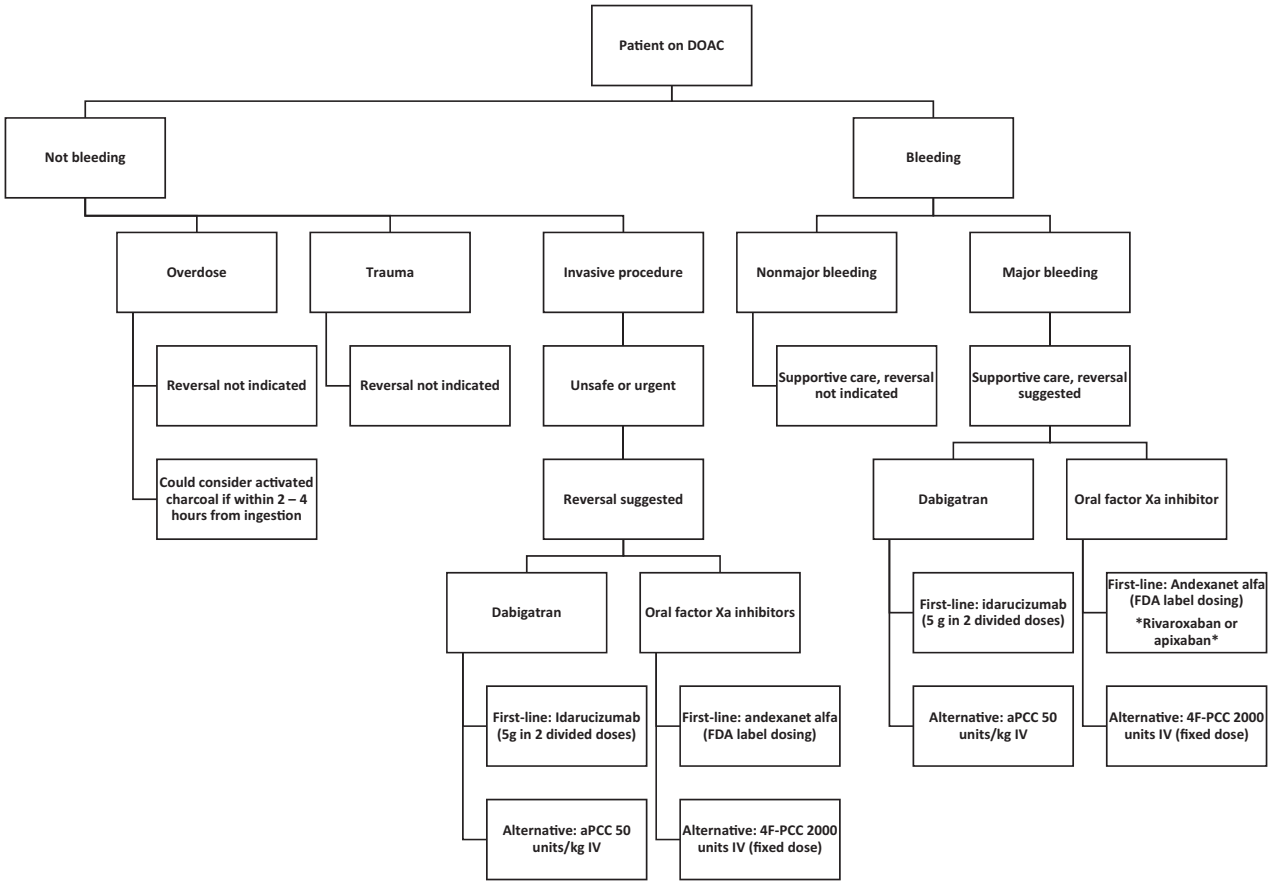

FIGURE 2 Summary of the reversal of direct oral anticoagulants (adapted guidance from the anticoagulation forum and 2020 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants)[45]

metabolism via CYP3A4 and all of the DOACs are substrates of P-gp.[11] As such, CNIs and DOACs have the potential of either being the perpetrator or target drug in a DDI. Although the FDA labeling of DOACs specify contraindications and dosing recommendations in concomitant use with a strong CYP3A4 and/or P-gp inhibitor, pharmacokinetic interactions with moderate CYP3A4 and/or P-gp inhibitors and the associated risk of bleeding are not well defined.[69,70]

The potential DDI between rivaroxaban and CNIs has been reported by three different groups in heterogeneous patient populations. Each case series noted that rivaroxaban may accumulate in the setting of CNI use but other confounders such as decreases in renal function may also play a role.[19,21,25] Researchers[71] investigated the DDIs between CNIs and apixaban in healthy volunteers. Co-administration of 100 mg of cyclosporine resulted in an increase in the apixaban C_{max} by the geometric mean ratio (GMR) of 1.43 [90% CI 1.12–1.83] but not in the apixaban area of the curve (AUC) (GMR 1.20, 90% CI 0.97–1.48). Co-administration with tacrolimus 5 mg resulted in reduced apixaban AUC (GMR 0.78, 90% CI 0.63–0.97) but no change in C_{max} (GMR 0.87, 90% CI 0.69–1.12). Although this study was unable to comment on the mechanism for the above variability, the magnitude of differences in AUC and C_{max} are not clinically significant. Another group[72] studied healthy subjects receiving a single oral dose of 60 mg edoxaban with or without cyclosporine 500 mg as a single dose. Co-administration with cyclosporine increased the edoxaban AUC by 73% and the C_{max} by 74%. In each of these cases, the relative changes in drug exposure were thought not to be clinically significant to warrant a dose adjustment. Even though cyclosporine has been implicated as having the greater potential for a DDI with the DOACs, registry data from the Taiwan National Health Insurance database did not find an association with increased risk of bleeding in patients receiving cyclosporine (n = 567) versus those without.[69]

Researchers[24] investigated whether DOACs can be considered the perpetrator drug and CNIs the victim drug in a single-center retrospective analysis including 39 organ recipients (18 kidney, 13 lung, and five heart) treated with the combination of a CNI and rivaroxaban (n = 29) or apixaban (n = 10). Rivaroxaban may cause a clinically insignificant (<20%) increase in CNI trough concentration, making it practical to repeat the CNI trough concentration measurement 5–7 days after DOAC initiation in select patients. A study[20] reported no significant difference in the mean CNI trough/dose ratio in liver transplant recipients at 30 days following DOAC initiation regardless of tacrolimus (p = 0.53) or cyclosporine use (p = 0.50). Further, another group[22] reported no changes in serum tacrolimus levels three days after the initiation of DOACs among kidney transplant recipients treated with tacrolimus (pre- and post-DOAC serum tacrolimus concentration was 7.35 and 7.80 ng/ml, p = 0.55).

5.2 | Concomitant use of azole antifungals

Azole antifungals are routinely used in SOT recipients for fungal prophylaxis and are considered either moderate inhibitors (fluconazole) or strong inhibitors (itraconazole, posaconazole, and voriconazole) of CYP3A4.[68] Currently, no controlled studies with azole antifungals exist to assess the risk of bleeding in patients concomitantly receiving DOACs and there was no uniform clinical approach to managing these interactions in the studies reviewed herein.[17–25] It was found[69] in a large retrospective cohort study that fluconazole increased the risk of major bleeding in patients concomitantly receiving a DOAC (dabigatran, rivaroxaban, and apixaban). Given the paucity of data, no empiric adjustment to DOAC dose can be recommended for concomitant use of an azole antifungal alone in patients with preserved renal function. However, the cumulative impact of this potential DDI in a patient with impaired renal function warrants individualized dose considerations. The apixaban prescribing information recommends a 50% dose decrease when coadministered with drugs that are strong dual-inhibitors of CYP3A4 and P-gp including ketoconazole and itraconazole, but it is unclear if this recommendation extends to posaconazole, voriconazole and isavuconazole.[73] Drug-specific monitoring may be beneficial in patients with DDI and/or impaired clearance.

5.3 | Concomitant use of antiplatelet agents

Mounting data from large registries have revealed an increased risk of bleeding in patients concomitantly receiving DOACs and an add-on antiplatelet agent versus those without.[70,74] Although a meta-analysis of the DOAC NVAF trials and registry data in patients with anticoagulation and concomitant antiplatelet agents suggests the use of DOACs with aspirin has less bleeding than VKA plus the addition of aspirin.[75,76] Further, randomized data from patients with NVAF who underwent percutaneous coronary intervention demonstrate that the use of DOACs and P2Y12 inhibitors together has a similar efficacy and potentially reduced risk of bleeding comparatively to warfarin plus P2Y12 inhibitors.[76–79]

It should be noted that in all of the peer-reviewed literature of DOAC use post-transplant there is a significant amount of empiric dose-adjustments being made (6%–100%).[17] This appears to be based on a variety of factors including potential pharmacokinetic and pharmacodynamic interactions, renal and hepatic dysfunction, and other clinical indicators of bleeding risk. In the absence of controlled clinical trials, empiric dose-adjustments for presumed pharmacokinetic or pharmacodynamic interactions is not recommended. Rather, DOAC prescribing in SOT recipients should be congruent with the FDA labeling recommendations.

5.4 | DOAC dosing in obese patients

Obesity in SOT recipients is common, as many patients with end-stage organ disease have a component of the metabolic syndrome. No large randomized controlled trial exists investigating the efficacy and safety of the DOACs in obese or morbidly obese patients. Therefore, clinicians are left to make treatment decisions from discordant pharmacokinetic/pharmacodynamic studies, retrospective studies, post-hoc analyses of phase III trials, and meta-analyses.[80–92]

Given that routine monitoring of DOAC concentrations is difficult to interpret and may be subject to variability, DOACs are not recommended in obese patients defined as a body mass index (BMI) ≥40 kg/m^2 and weight ≥120 kg.[93] In-depth considerations in morbidly obese patients and the data since the Scientific and Standardization Committee (SSC)/ISTH recommendation have been reviewed previously in this Journal.[94] Since this publication, there have been two additional meta-analyses assessing the rate of stroke or systemic embolism (SSE) and major bleeding in NVAF patients with obesity and morbid obesity.[92]

Researchers[92] stratified NVAF patients based on BMI category and whether patients received a DOAC or warfarin and found no difference in SSE (relative risk [RR] 0.87, 95% CI 0.73–1.04) or major bleeding (RR 0.90, 95% CI 0.81–1.01) in patients receiving a DOAC or warfarin with BMI category ≥30 kg/m^2. A second group specifically focused the meta-analyses on patients with morbid obesity (BMI >40 kg/m^2 or weight >120 kg) and found no difference between DOACs and warfarin for SSE (OR 0.85, 95% CI 0.60–1.19), but less major bleeding (OR 0.63, 95% CI 0.43–0.94) in patients receiving DOACs. Of note, there were no differences in major bleeding between those who received apixaban versus rivaroxaban.[95] Given the lack of pharmacokinetic/pharmacodynamic data in patients who are both transplant recipients and obese, the use of DOACs in obese SOT patients should be used with caution.

5.5 | DOAC dosing in hemodialysis patients

The 2019 update to the American Heart Association (AHA)/ACC/Heart Rhythm Society (HRS) 2014 guideline suggests the use of warfarin or apixaban for patients with atrial fibrillation on dialysis may be reasonable if a CHA_2DS_2 -VASc score is ≥2 in men or ≥3 in women.[96] Despite patients on hemodialysis being excluded from registration trials, the use of DOACs in patients on hemodialysis has been attempted. With the exception of apixaban, the FDA labeling for each DOAC recommends against use in patients on hemodialysis.[97]

Both a 10- and a 15-mg dose of rivaroxaban has been evaluated in single-dose studies in hemodialysis patients, but meta-analyses suggest that there are higher rates of bleeding when rivaroxaban is used for NVAF patients on hemodialysis.[98–102] Apixaban, on the other hand, undergoes significantly less renal clearance and has pharmacokinetic data to support its use in hemodialysis.[103] Additionally, since the publication of the guideline two additional meta-analyses support the use of apixaban in hemodialysis.[101,102] Unfortunately, the much anticipated RENAL-AF trial that randomized hemodialysis patients to either apixaban 5 mg twice a day (BID) or warfarin was stopped early due to slow enrollment.[104]

While the available data point at a relative benefit in safety of apixaban versus warfarin in patients on hemodialysis, a definitive clinical trial is lacking to determine the best anticoagulant in this patient population awaiting transplant. Moreover, heterogeneity exists between the data supporting apixaban 2.5 mg BID versus 5 mg BID for patients on hemodialysis without other reasons for a dose-adjustment. Pharmacokinetic data from patients taking apixaban 2.5 mg BID on hemodialysis demonstrated comparable drug exposure to that of the 5 mg BID dose in patients with preserved renal function. Further, after a washout period, the same patients received apixaban 5 mg BID and a further increase was noted above the 90th percentile compared with the reference value generated in patients with preserved renal function.[105] This is in contrast to clinical data from retrospective cohort study exploring the United States Renal Data System that analyzed hemodialysis patients taking either apixaban or warfarin for NVAF. In a sensitivity analysis, the 5 mg BID dose was associated with significantly lower risks of stroke or systemic embolism and death as compared to either the reduced dose of 2.5 mg BID or warfarin.[103] Recently, a meta-analysis of observational studies compared DOACs versus warfarin versus no anticoagulation and found no benefit of either DOACs or warfarin versus no anticoagulation for NVAF patients on hemodialysis. However, in the sensitivity analysis, the 5 mg BID dose had no difference in major bleeding and a reduction in mortality when compared to the 2.5 mg BID dose.[101]

As most patients on hemodialysis with atrial fibrillation will have an elevated CHA_2DS_2VASc score, it is reasonable to follow the FDA labeling recommendation of apixaban 5 mg BID, as this has shown benefit in available registry data and a meta-analysis studies.[97,101,103] However, each patient's risk of bleeding and clotting should be scrutinized prior to choosing either 2.5 mg or 5 mg BID. Drug-specific monitoring may be beneficial to avoid complications of supra-therapeutic anticoagulation.

6 | CONCLUSION

Given the absence of prospective, randomized, controlled trials investigating safety and efficacy of DOACs in SOT recipients, this review highlights four important retrospective observational studies comparing DOACs to VKAs in SOT recipients. In these studies, the incidence of bleeding with DOACs was similar, if not lower, to that of VKAs. Based on these findings, DOACs, particularly apixaban, are safe and effective alternatives to VKAs. In the studies discussed, DOAC doses were often reduced based on clinical factors. This review discusses pharmacokinetic considerations for DOACs relating to dose adjustments, DDIs, weight, and renal function. Given that none of these factors alone warrant DOAC dose adjustments, FDA labeling for DOAC dose adjustments should be followed. In cases where multiple factors are present that may increase DOAC concentrations, clinical discretion should be utilized. Although novel agents for DOAC reversal in the setting of life-threatening bleeding have emerged, DOAC use in the pre-transplant setting remains controversial given the absence of a standardized approach for periprocedural DOAC reversal. Utilization of andexanet alfa in the setting of pre-transplant reversal should be carefully considered on an individual patient basis and a universal use of reversal agents in this setting cannot be recommended based on the current paucity of literature and potential thrombosis risk. Clinicians must consider the phase of transplant, DDIs, weight, and renal function in order to determine the optimal anticoagulant for a transplant candidate or recipient.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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