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Direct oral anticoagulants versus warfarin in adult heart transplant recipients

Lauren Shitanishi, PharmD,[a,*] Ashley Fan, PharmD,[a] Tam Khuu, PharmD,[a] Darko Vucicevic, MD,[a] Megan Kamath, MD,[a] Jeffrey J. Hsu, MD, PhD,[a] Alexandra Klomhaus, PhD,[a] and Reza Ardehali, MD, PhD[b,c,**]

[a]*University of California Los Angeles Medical Center, Los Angeles, California*
[b]*Baylor College of Medicine, Department of Medicine, Section of Cardiology, Houston, Texas*
[c]*Texas Heart Institute, Houston, Texas*

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BACKGROUND: Direct oral anticoagulants (DOACs) have transformed the field of anticoagulation, offering more predictable pharmacokinetic and pharmacodynamic characteristics when compared to traditional warfarin therapy. DOAC use in the heart transplant population is particularly important to further study due to the high risk of venothromboembolism and the potential for significant drug interactions and altered pharmacokinetics post-transplantation.

METHODS: A single center, retrospective cohort study was performed in adult heart transplant recipients requiring anticoagulation following transplantation between January 2010 and July 2021. Primary outcomes included incidence of bleeding and breakthrough thromboembolic events.

RESULTS: Ninety-five patients met inclusion criteria and out of these patients, 30 (32%) were prescribed warfarin and 65 (68%) were prescribed a DOAC. Seventeen total bleeding events occurred. Bleeding events were significantly more common in the warfarin group compared to the DOAC group (58% vs 41%, $p = 0.0077$). There was a total of 6 breakthrough thrombotic events in this cohort, all of which were patients on DOAC therapy.

CONCLUSION: DOAC therapy in heart transplant recipients may be safer from a bleeding perspective when compared to warfarin. Additional data to further evaluate the appropriateness for dose modifications for patients with potential drug-drug interactions, higher bleed risk, and unstable renal function are needed to guide optimal practice and dosing strategies in heart transplant recipients.

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Background

Direct oral anticoagulants (DOACs) offer pharmacokinetic advantages when compared to warfarin, including shorter half-lives, lower inter and intrapatient variability, no required routine laboratory monitoring, and fewer potential drug and food interactions.[1] Although DOACs are the preferred anticoagulant vs warfarin for the treatment of venous thromboembolism (VTE) and nonvalvular atrial fibrillation in the general population,[2] data regarding the use

*Corresponding author: Lauren Shitanishi, PharmD, University of California Los Angeles Medical Center, 757 Westwood Plaza, Los Angeles, CA 90095.

**Corresponding author: Reza Ardehali, MD, PhD, Baylor College of Medicine, Department of Medicine, Section of Cardiology, Houston, TX 77030.

E-mail addresses: lauren.shitanishi@cshs.org, Reza.Ardehali@bcm.edu.

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of DOACs in comparison to warfarin in the solid organ transplant population remain limited.

Heart transplant recipients are known to be at increased risk for VTE, and several studies have noted significantly higher rates of VTE when compared to the general population.[3,4] This increased risk, especially within the first year post-transplant, can be due to the need for frequent endomyocardial biopsies, altered hemostasis, and use of medications, such as mammalian target of rapamycin (mTOR) inhibitors.[5] In addition to the increased VTE risk, the heart transplant population is particularly important to further study due to the potential for altered pharmacokinetics and significant drug interactions. There is no clear consensus on the safety and efficacy of the use of DOACs in heart transplant. Additionally, there is a lack of data on how to appropriately manage DOACs with regard to drug interactions and dosing within this patient population which may leave clinicians wary of prescribing DOACs.

This study aims to further evaluate the safety and efficacy of anticoagulants in adult heart transplant recipients and characterize their use in this unique patient population.

Methods

Study design

This single-center, retrospective cohort study included all adult heart transplant recipients (> 18 years) from an academic medical center between January 2010 and July 2021. This study was approved by the UCLA Institutional Review Board (#21-000362). Patients were included if they were prescribed a DOAC (apixaban, rivaroxaban, dabigatran, or edoxaban) or warfarin following heart transplantation. Patients were excluded for incomplete data or lost follow-up.

Data were collected from the shared electronic medical record. The primary objective was to compare the incidence of bleeding events and breakthrough thrombotic events between patients on warfarin compared to those on DOAC therapy. The secondary objectives were to characterize the use and describe prescribing patterns at our center. Patients were reviewed for the entire duration of their anticoagulation therapy or until last follow-up if still on anticoagulation therapy. Anticoagulant use was defined as the first agent used—clinical outcomes were not assessed further if a patient was switched to a different anticoagulation regimen. Major and minor bleeding events were defined using the International Society on Thrombosis and Haemostasis classifications.[6] Package label dosing is defined as the Food and Drug Administration (FDA)-approved drug manufacturer dosing regimen. For patients on warfarin, international normalized ratio was captured on the day of the documented bleeding event. Anti-Xa assays were not used to monitor patients on DOAC therapy.

Transplant medication management

All patients receive standard triple immunosuppression therapy with tacrolimus, mycophenolate mofetil, and steroids post-transplant per institutional protocol. Any changes to the standard immunosuppression regimen were based on patient-specific risk factors and physician preference. All recipients are prescribed aspirin 81 mg daily indefinitely per protocol and sometimes discontinued if anticoagulation is initiated. All recipients receive antifungal prophylaxis with either a clotrimazole troche for 3 months or fluconazole indefinitely if recipients are from a coccidioidomycoses endemic area and/or are coccidioidomycosis IgG positive. All patients also receive *Pneumocystis jirovecci* prophylaxis for 1 year and viral prophylaxis for 3 to 12 months depending on cytomegalovirus risk.

Statistical analysis

We conducted all statistical analyses using SAS 9.4 (SAS Institute, Cary, NC). We generated descriptive statistics, including means and standard deviations for continuous variables and counts and frequencies for categorical variables, for baseline demographic and clinical characteristics among the analytical sample. We present these statistics both overall and stratified by warfarin or DOAC. To compare characteristics between groups, we used chi-square tests (or Fisher's exact tests) for categorical variables and Wilcoxon 2-sample tests for continuous variables and report associated *p*-values. We then limited our sample to only those with a bleed event (our primary outcome) and completed the same set of stratified descriptive statistics and 2-group comparisons between warfarin and DOAC.

To describe time-to-event, with event being a bleed, while accounting for censoring, we calculated product-limit survival estimates and used the log-rank test to assess equality over the 2 groups (warfarin vs DOAC). We present both a graphical depiction of the Kaplan-Meier curves, as well as the associated log-rank chi-square *p*-value.

Results

A total of 95 heart transplant recipients were prescribed anticoagulation post-transplant with either warfarin or a DOAC between January 2010 and July 2021. Thirteen of these patients were dual-organ transplant recipients—2 heart-liver and 11 heart-kidney. There was a total of 540 adult heart transplants performed during this time. Out of 95 patients, 30 (32%) received warfarin and 65 (67%) received a DOAC. The most common DOAC prescribed was apixaban (n = 52) followed by rivaroxaban (n = 12) and dabigatran (n = 1). There were no significant differences in baseline characteristics between groups (Table 1). The most common indication for anticoagulation in both groups was deep vein thrombosis followed by pulmonary embolism, atrial fibrillation, and genetic mutations predisposing to thrombosis. Other indications included events such as hepatic vein thromboses, stroke, cardiac thromboses, and ventricular tachycardia ablation prophylaxis.

Bleeding events

There was a total of 17 bleeding events that occurred in this study. Bleeding events were significantly more common in the warfarin group compared to the DOAC group (58% vs 41%, p = 0.0077) (Table 2). There were no significant differences in bleeding event characteristics between groups (Table 3). The most common source of bleeding was gastrointestinal (22%), followed by intracranial (16%) and vaginal/uterine (16%). Other bleeding sources included hematomas, pericardial effusions, and severe epistaxis (Supplementary Appendix I). Out of the patients who had

Table 1 Patient Demographics and Characteristics

Characteristic	Overall (N = 95) N (%[a])	Warfarin (N = 30) N (%)	DOAC (N = 65)	*p*-value[b]
Age (years) at anticoagulation initiation, mean (sd)	53.0 (15.9)	51.4 (15.3)	53.7 (16.2)	0.4605
Male	66 (69.5)	19 (63.3)	47 (72.3)	0.3373
Race				0.5126
White	43 (45.3)	16 (53.3)	27 (41.5)	
Black/African American	12 (12.6)	4 (13.3)	8 (12.3)	
Asian	8 (8.4)	3 (10.0)	5 (7.7)	
Other	32 (33.7)	7 (23.3)	25 (38.5)	
Body mass index (BMI), mean (sd)	26.1 (5.0)	26.5 (5.5)	25.9 (4.8)	0.7374
Indication				
Lower extremity DVT	29 (30.5)	10 (33.3)	19 (29.2)	0.6865
Upper extremity DVT	34 (35.8)	8 (26.7)	26 (40.0)	0.2076
Pulmonary embolism	17 (17.9)	6 (20.0)	11 (16.9)	0.7161
Atrial fibrillation	9 (9.5)	2 (6.7)	7 (10.8)	0.7146
Genetic mutation	6 (6.3)	3 (10.0)	3 (4.6)	0.3760
Other	17 (17.9)	5 (16.7)	12 (18.5)	0.8320
Duration of therapy (days), mean (sd)[c]	433.7 (572.7)	416.4 (504.5)	441.8 (605.2)	0.8952
Concomitant antiplatelet use				
Yes (any)	45 (47.3)	18 (60.0)	27 (41.5)	0.0939
Aspirin	41 (43.2)	15 (50.0)	25 (38.5)	0.0674
Clopidogrel	2 (2.1)	—	2 (3.1)	
Ticagrelor	1 (1.1)	1 (3.3)	—	
Aspirin and clopidogrel	—	—	—	
Renal function				
SCr (mg/dl), mean (sd)	1.4 (1.0)	1.5 (1.2)	1.4 (0.8)	0.5154
Hemodialysis	5 (5.3)	3 (10.0)	2 (3.1)	0.3215
Concomitant azole antifungal use				0.2707[e]
Fluconazole	54 (56.8)	16 (53.3)	38 (58.5)	
Clotrimazole	23 (24.2)	5 (16.7)	18 (27.7)	
Posaconazole	3 (3.2)	2 (6.7)	1 (1.5)	
Voriconazole	2 (2.1)	1 (3.3)	1 (1.5)	
None	13 (13.7)	6 (20.0)	7 (10.8)	
Induction				0.0988[e]
Antithymocyte globulin (rabbit)	14 (14.7)	3 (10.0)	11 (16.9)	
Basiliximab	29 (30.5)	15 (50.0)	14 (21.5)	
None	52 (54.7)	12 (40.0)	40 (61.5)	
Hepatic function				
AST	29.5 (29.3)	29.8 (35.4)	29.4 (26.3)	0.6547
ALT	27.4 (24.6)	28.5 (21.8)	26.9 (25.9)	0.8983
Alk Phos	95.0 (42.1)	93.8 (44.6)	95.5 (41.2)	0.8200
T bili	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.9021

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DOAC, direct oral anticoagulants; DVT, deep vein thrombosis.
[a](%) = column percentage.
[b]*p*-value from chi-square test (or Fisher's exact test) for categorical variables, Wilcoxon test for continuous variables.
[c]Includes those who are still on therapy using date of last observation/record.
[e]"None" excluded from test for association.

Table 2 Outcomes

Primary outcomes	Overall (N = 95)	Warfarin (N = 30)	DOAC (N = 65)	*p*-value[b]
Any bleeding events	17 (17.9)	10 (33.3)	7 (10.8)	0.0077
Any breakthrough thrombotic events	6 (6.3)	0 (0.0)	6 (9.2)	0.1720

[b]*p*-value from chi-square test (or Fisher's exact test) for categorical variables, Wilcoxon test for continuous variables.

bleeding events, all patients on warfarin had either subtherapeutic or within-range international normalized ratio on the day of the bleeding event. Additionally, out of the patients with documented bleeding events, 57% of patients on DOACs and 40% of patients on warfarin were also on concomitant azole antifungal and antiplatelet therapy. None of the azole antifungals used concomitantly with DOACs in the bleeding group required DOAC dose adjustments per package label dosing recommendations, and all DOACs were dosed appropriately according to these recommendations (Table 4).

Table 3 Bleeding Event Characteristics

Characteristic	Overall (N = 17) N (%[a])	Warfarin (N = 10) N (%)	DOAC (N = 7) N (%)	*p*-value[b]
Bleeding events classification				1.0000
Major	7 (41.2)	4 (40.0)	3 (42.9)	
Minor	10 (58.8)	6 (60.0)	4 (57.1)	
Source of bleed				0.2542
Gastrointestinal	4 (23.5)	3 (30.0)	1 (14.2)	
Intracranial	3 (17.7)	1 (10.0)	2 (28.6)	
Vaginal/uterine	2 (11.8)	—	2 (28.6)	
Other	8 (47.1)	6 (60.0)	2 (28.6)	
Blood transfusion required	6 (35.3)	3 (30.0)	3 (42.9)	0.6437
Reversal agent required	4 (23.5)	3 (30.0)	1 (14.3)	0.6029
Time from anticoagulation start to bleeding event (days), mean (sd)	284.9 (476.6)	272.1 (416.3)	303.1 (587.4)	0.8854
Time from transplant to bleeding event (days), mean (sd)	1038.5 (1340.1)	933.1 (1007.9)	1189.1 (1794.5)	0.8854
Interacting medications				0.7797
Antiplatelet	4 (23.5)	3 (30.0)	1 (14.3)	
Azole antifungal	3 (17.7)	2 (20.0)	1 (14.3)	
Antiplatelet and azole antifungal	8 (47.1)	4 (40.0)	4 (57.1)	
Dual antiplatelet	1 (5.9)	1 (10.0)	—	
None	1 (5.8)	—	1 (14.3)	
Deviation from package label dosing	4 (23.5)	—	4 (57.1)	N/A
Action following event				0.6082
Discontinue	4 (23.5)	3 (30.0)	1 (14.3)	
Dose change/medication change	4 (23.5)	1 (10.0)	3 (42.9)	
Hold and resume	6 (35.3)	4 (40.0)	2 (28.6)	
None	3 (17.7)	2 (20.0)	1 (14.3)	

[a](%) = column percentage.
[b]*p*-value from chi-square test (or Fisher's exact test) for categorical variables, Wilcoxon test for continuous variables.

Kaplan-Meier curves for time-to-bleed events, stratified by warfarin and DOAC, are found in Figures 1 and 2. Results from a log-rank test suggest significantly different survival curves between strata (chi-square = 6.66, $p = 0.0099$), where "survival" refers to time without a bleed event. Notably, patients on warfarin had significantly faster time-to-bleed compared to patients on a DOAC, or equivalently, patients on a DOAC had significantly more time without a bleed event compared to patients on warfarin, when accounting for censoring.

Breakthrough thrombotic events

There was a total of 6 breakthrough thrombotic events in this cohort, all of which included patients on DOAC therapy (Table 2). Breakthrough thrombotic events included ischemic stroke, pulmonary embolism, and new or worsening VTE. Four out of 6 patients who had breakthrough thrombotic events were on reduced doses, which deviated from the recommended package label dosing regimen. All 4 of these patients were on apixaban 2.5 mg twice daily opposed to the recommended 5 mg daily and did not receive loading doses. Out of all the patients in our cohort on DOACs with or without breakthrough thrombotic events ($n = 65$), 41 (63%) were prescribed dosing regimens that deviated from package labeling dosing—13 of these patients received dose adjusted maintenance regimens and 38 did not receive indicated loading doses. Out of the 41 patients on these adjusted regimens, only 4 (9.8%) experienced breakthrough thrombotic events as mentioned above while the other 37 patients did not.

Table 4 Breakthrough Thrombotic Event Characteristics

Characteristic	Overall (N = 6) N (%[a])	DOAC (N = 6)
Deviation from package labeling dosing	4 (66.7)	4 (66.7)
Interacting medications		
Azole antifungal	3(50.0)	3 (50.0)
Antiplatelet and azole antifungal	3 (50.0)	3 (50.0)
Time from anticoagulation start to breakthrough thromboembolic event (days), mean (sd)	411.3 (779.5)	411.3 (779.5)
Time from transplant to breakthrough thromboembolic event (days), mean (sd)	482.2 (851.6)	482.2 (851.6)

[a](%) = column percentage.

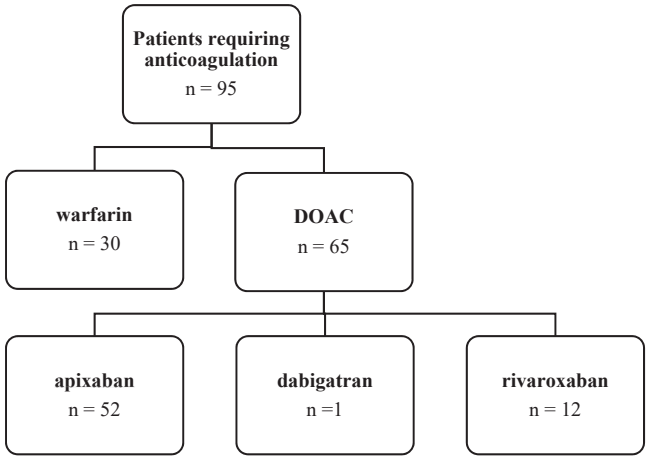

Figure 1 Distribution of patients on warfarin vs DOACs. DOAC, direct oral anticoagulant.

Discussion

Our study demonstrates that heart transplant recipients on warfarin post-transplant have a higher bleeding risk when compared to those on a DOAC, but there may be a trend toward higher rethrombosis rates for patients on DOACs if not appropriately dosed. This study identified higher prescribing rates of DOACs overall, with apixaban as the most utilized in our heart transplant recipients despite its FDA approval only in 2012, just 2 years after the initiation of our study. This trend shows the recent increased interest in DOACs given the absent need for drug monitoring and further emphasizes that when appropriately dosed, a DOAC may be an easier and safer option compared to warfarin in heart transplant recipients given the lower bleeding risk found in our study.

It may be difficult at times to follow strict DOAC dose adjustments based on package label dosing recommendations in the heart transplant population. Providers are often more conservative with anticoagulation dosing strategies due to poor or fluctuating renal function, higher bleeding risk, and/or interacting transplant medications. For this patient population, the Heart Transplant team determined anticoagulation agent and dosing regimen for each patient case. Dosing was ultimately determined at the provider's discretion and was the reason for dose modifications. Azole antifungal use is important to discuss further as many transplant patients are commonly prescribed these agents due to their increased infection risk while on immunosuppression. All azole antifungals have varying degrees of CYP3A4 and P-glycoprotein inhibition, and since DOACs are substrate inducers, it is important to consider this when determining appropriate DOAC dose adjustments. In a similar study by Lichvar et al,[7] DOAC dose reduction in their cardiothoracic transplant cohort was common (59.4%) due to drug-interactions and renal dysfunction. Additionally, transplant patients on lifelong calcineurin inhibitor therapy are at increased risk for chronic

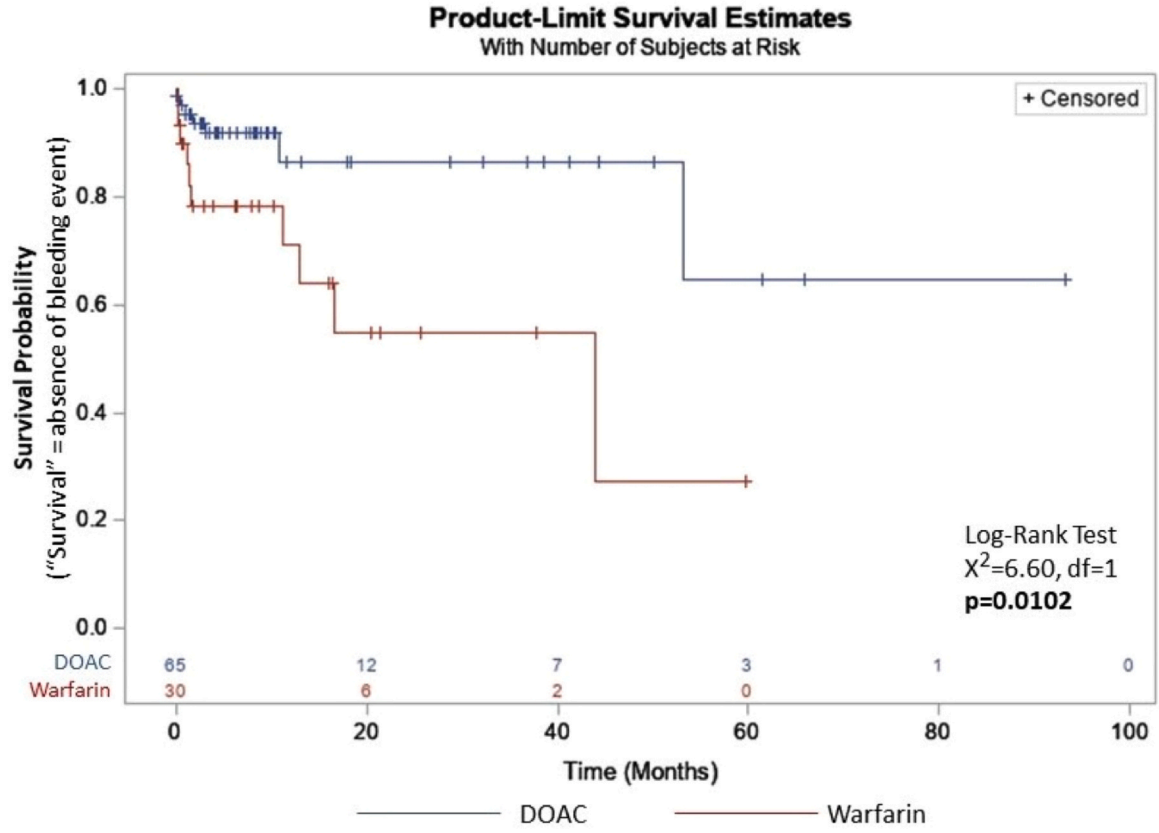

Figure 2 Kaplan-Meier curves illustrating time-to-bleed or censoring (defined as end-of-therapy), stratified by DOAC and warfarin, with the number of subjects at risk by group. DOAC, direct oral anticoagulant.

renal failure, further putting them at risk for drug toxicity and bleeding. The need for biopsy monitoring in heart transplant recipients may also be a factor in reduced DOAC doses or avoiding their use altogether. All these factors can be reasons for favoring a more conservative dosing strategy, which can be difficult to determine when also weighing thrombotic risk.

Several small retrospective cohort studies have evaluated the use of DOACs compared to warfarin in solid organ transplant recipients.[8–10] All studies found no significant difference in bleeding or breakthrough thrombotic events. Henricksen et al[9] reported that patients on DOACs had fewer bleeding events than those on warfarin (10% vs 23%, $p = 0.08$) and a significantly lower risk for requiring blood transfusions compared to warfarin ($p = 0.04$). It was identified, however, that 2 patients experienced breakthrough thrombosis, possibly due to reduced dose of DOAC therapy as a result of the drug interaction with itraconazole. Our study adds to the current literature by further identifying the trend toward increased bleeding risk with warfarin and more breakthrough thrombotic events in patients who were prescribed DOACs possibly related to dose reductions. Patients in our study experienced less bleeding with DOACs but did have deviations in dosing as mentioned above for a variety of reasons, including drug interactions, renal dysfunction, and lack of familiarity of treating physicians. Additionally, with the 2023 International Society of Heart and Lung Transplantation guidelines now recommending DOACs as an alternative to warfarin in heart transplant recipients,[11] it is important to continue to assess outcomes in these patients on these therapies.

Several limitations exist within this study. This was a single-center, retrospective cohort study utilizing data from electronic medical records—our data were dependent on the available information and may have been under-reported or missed if not documented. Additionally, there was no power analysis performed for the small sample size, and there were few bleeding/thrombotic outcome events for analysis. Finally, the decreased number of bleeding events in DOAC treatment arm must be carefully weighed due to the significant number of patients who had dose reductions that do not align with package labeling recommendations. Additional data may be needed to describe the safety of appropriately dosed DOACs when compared to warfarin.

Despite the above limitations, this is the largest cohort to date comparing warfarin and DOAC use in heart transplant recipients. In addition to the available literature, our study provides further insight into the prescribing patterns of DOACs as well as bleeding outcomes compared to warfarin in this specific patient population.

Conclusion

DOAC therapy in heart transplant recipients may be safer from a bleeding perspective when compared to warfarin. However, providers should continue to carefully consider which clinical scenarios would be appropriate for empiric dose reductions with DOACs to avoid inappropriate dose adjustments and potential breakthrough thrombotic events on therapy. Additional data to further evaluate the appropriateness for dose modifications for patients with potential drug-drug interactions, higher bleed risk, and unstable renal function are needed to guide optimal practice and dosing strategies in heart transplant recipients.

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Ninety-seven heart transplant recipients were prescribed anticoagulation with a DOAC or warfarin. There were more bleeding events in the warfarin group (61% vs 39%, $p = 0.0049$) and numerically more breakthrough thrombotic events in the DOAC group (86% vs 14%, $p = 0.4917$).

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100061.

References

1. Garcia-Ortega A, López-Reyes R, Anguera G, et al. Venous thromboembolism in solid-organ transplant recipients: findings from the RIETE registry. Thromb Res 2021;201:131-8.
2. Kearon C, Akl E, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. CHEST 2016:315-52.
3. Alvarez-Alvarez RJ, Barge-Caballero E, Chavez-Leal SA, et al. Venous thromboembolism in heart transplant recipients: incidence, recurrence and predisposing factors. J Heart Lung Transplant 2015;34:167-74.
4. Elboudwarej O, Patel JK, Liou F, et al. Risk of deep vein thrombosis and pulmonary embolism after heart transplantation: Clinical outcomes comparing upper extremity deep vein thrombosis and lower extremity deep vein thrombosis. Clin Transplant 2015;29:629-35. https://doi.org/10.1111/ctr.12566.
5. Rizk J, Mehra MR. Anticoagulation management strategies in heart transplantation. Prog Cardiovasc Dis 2020;63:210-8.
6. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
7. Lichvar AB, Moore CA, Ensor CR, McDyer JF, Teuteberg JJ, Shullo MA. Evaluation of direct oral anticoagulation therapy in heart and lung transplant recipients. Prog Transplant 2016;26:263-9.

8. Hazelcorn J, Yau R, Sabagha N, Moaddab M, Manson M. Risk of major bleeding in solid organ transplant recipients taking calcineurin inhibitors concomitantly with direct oral anticoagulants compared to warfarin. Am J Transplant 2017;17(Suppl 3).
9. Henricksen EJ, Tremblay-Gravel M, Moayedi Y, et al. Use of direct oral anticoagulants after heart transplantation. J Heart Lung Transplant 2020;39:399-401.
10. Kim M, Gabardi S, Townsend KR, Page DS, Woodcome EL, Givertz MM. Post transplant thrombosis and atrial arrhythmia may be safely managed by direct oral anticoagulants in cardiac transplant patients. J Heart Lung Transplant 2016;35:S123.
11. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2023;42:e1-141.