ORIGINAL ARTICLE

# Safety and efficacy of direct-acting oral anticoagulants versus warfarin in kidney transplant recipients: a retrospective single-center cohort study

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## SUMMARY

Despite the increased use, comparative safety and efficacy of direct-acting oral anticoagulants (DOACs) against warfarin have not been well studied in kidney transplant recipients. In this single-center retrospective study, we evaluated 197 adult kidney transplant recipients on DOAC or warfarin between January 1, 2011, and June 30, 2018. The primary outcome was incidence of major bleeding defined as a hemoglobin decrease ≥2 g/dl, blood transfusion ≥2 units, or symptomatic bleeding in a critical area or organ. Patients were initiated on anticoagulation therapy at a median of 6.5 years post-transplant and followed for a median of 12.3 months. The rates of major bleeding were 7.2% per year with DOACs vs. 11.4% per year with warfarin (Mantel–Cox $P = 0.15$). No difference was found in composite bleeding, clinically relevant nonmajor bleeding, or thromboembolic events between the groups. There was a lower incidence of major bleeding with apixaban compared to all other anticoagulants (6.7% vs. 19.0%, $P = 0.027$). After controlling for potential confounders, DOAC use was not associated with an increased risk of major bleeding (HR 0.73, 95% CI 0.27–1.95). Further research is warranted to definitively determine whether DOACs are effective and safe alternatives to warfarin for anticoagulation in kidney transplant recipients.

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**Key words**
anticoagulation, direct oral anticoagulant, kidney transplant, major bleeding, vitamin K antagonist

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## Introduction

Direct-acting oral anticoagulants (DOACs) have become more commonly prescribed since the approval of dabigatran in 2010 and have significantly impacted anticoagulation management for venous thromboembolism (VTE) and stroke prevention in atrial fibrillation [1]. Their unique mechanism of action and pharmacokinetic properties provide advantages and disadvantages compared with the historical oral anticoagulant of choice, warfarin [2]. Advantages include infrequent laboratory monitoring, and predictable pharmacokinetic and pharmacodynamic characteristics thereby allowing for fixed oral doses. Because robust pharmacokinetics studies and clinical trials of these




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novel agents are lacking in patients with severe renal impairment, there is a hesitancy to use them in patients with diminished renal function or end-stage renal disease because of potentially increased bleeding risk.

The incidence of new-onset atrial arrhythmias after kidney transplantation has previously been reported to range from 2.6% to 7.6% [3,4]. Additionally, kidney transplant recipients are at an increased risk for VTE possibly because of impaired fibrinolysis and a heightened hypercoagulable state [5]. More importantly, the complications of atrial arrhythmias and VTEs can result in graft failure, morbidity, and mortality [6]. Thus, medical management becomes crucial in this patient population. While appealing to use, there are significant barriers to the appropriate use of DOACs in the kidney transplant population, including an accurate estimation of glomerular filtration rate (GFR) and drug–drug interactions. The equations that are used to estimate GFR after kidney transplantation are similar to that used in the general population, without accounting for recipient and graft related factors that may alter GFR, including, but not limited to coexisting diseases, selected medications, and graft blood flow [7]. In a transplant population where true renal function may be under or overestimated by conventional methods to calculate GFR, DOACs may be inappropriately dosed. Furthermore, drug–drug interactions including cytochrome P-450 (CYP) and P-glycoprotein (P-gp) inhibitors can result in adverse drug events. Calcineurin inhibitors (CNIs) such as cyclosporine and tacrolimus are maintenance immunosuppressive agents used to prevent rejection in the transplant population. Cyclosporine is recognized as a moderate inhibitor of CYP3A4 and P-gp and can potentially interact with substrates of CYP3A4 and P-gp such as DOACs [8]. Other medications including antiarrhythmics (e.g., amiodarone and diltiazem) and antifungals (e.g., fluconazole and voriconazole) that transplant patients may encounter post-transplant also interact with DOACs and further complicate anticoagulation management. The purpose of our study was to compare the safety and efficacy of DOACs to warfarin in kidney transplant recipients.

## Materials and methods

### Study design

This study was conducted as a single-center retrospective cohort study. The study cohort included adult kidney transplant recipients from Michigan Medicine with a functioning allograft who initiated DOAC therapy (apixaban, dabigatran, or rivaroxaban) or warfarin after transplantation between January 1, 2011, and June 30, 2018. Patients were excluded if any of the following criteria were met: multi-organ transplant recipients, anticoagulation treatment initiation prior to transplantation, patients with mechanical or prosthetic valves, gastrointestinal bleeding within six months prior to initiation of anticoagulation, anticoagulation indication other than VTE or atrial fibrillation, patients with incomplete records, or those anticoagulated for less than 30 days (if not discontinued for bleeding event). This study was approved by the Institutional Review Board of University of Michigan Medical School (HUM00092121).

The primary outcome of this study was the incidence of major bleeding defined by the International Society on Thrombosis and Haemostasis (ISTH): bleeding leading to a decrease in hemoglobin (Hgb) $\geq$2 g/dl at any time point, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular, or retroperitoneal bleed) [9]. If any of the previously mentioned criteria were met and not attributed to any other cause, it was determined that the patient had a major bleed because of anticoagulation therapy. The definition for clinically relevant nonmajor bleeding (CRNMB) was also consistent with ISTH recommendations: any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding but requires medical intervention by a healthcare professional, leads to hospitalization or increased level of care, or prompts a face to face (i.e., not just a telephone or electronic communication) evaluation [10]. Secondary outcomes included composite bleeding (major bleeding and CRNMB), new-onset or recurrent VTE, and new-onset stroke during anticoagulation therapy. Other measurable outcomes included drug–drug interactions and appropriate DOAC dosing according to renal function and indication. Appropriateness of dosing was defined by the U.S. Food and Drug Administration prescribing information for each DOAC [11-13]. A subanalysis was also planned to examine major bleeding risk among the DOACs. Patients were followed until major bleeding event, discontinuation of anticoagulation, death, or most recent laboratory value (for patients currently on anticoagulation), whichever occurred first. Since patients were followed until a first major bleeding event, repeat bleeding events would only be captured if a patient experienced a CRNMB event prior to a major bleeding event. Bleeding events were identified by reviewing Hgb values in the routine post-transplant laboratories, reasons for

emergency room visits and hospital admissions, and searching the electronic medical records using the search term "bleed." Prior bleeding events were defined as bleeding events reported in the past medical history that had occurred prior to the initiation of anticoagulation.

### Institutional pharmacologic management

All kidney transplant patients received a maintenance immunosuppression regimen consisting of tacrolimus or cyclosporine, and mycophenolate mofetil with steroids per institutional protocol at the time of transplantation. Subsequent changes in maintenance immunosuppressive regimens were individualized per providers. The goal tacrolimus trough was 8–12 ng/ml for the first 90 days post-transplant, 6–10 ng/ml during days 91–120, and 4–8 ng/ml after postoperative day 120. The goal cyclosporine trough was 250–300 ng/ml for postoperative days 0–90, 200–250 ng/ml for postoperative days 91–180, 150–200 ng/ml for postoperative days 181–365, and 100–200 ng/ml after one year. Transplant recipients were on fungal prophylaxis with oral nystatin solution for 1 month, viral prophylaxis for 3–6 months, and *Pneumocystis jirovecii* pneumonia prophylaxis for 1 month post-transplantation. Anticoagulation management was provider specific and not according to an institutional protocol. Prior to transplant listing, all patients received a routine colonoscopy per protocol.

### Statistical analysis

Normally distributed continuous variables were compared using the Student's t-tests and are presented as mean ± standard deviation (SD). Non-normally distributed continuous variables were analyzed using the Mann–Whitney *U* tests and are presented as median with interquartile range (IQR). Categorical variables are presented in percentage and were compared utilizing the chi-square or Fisher's exact tests. Time to major bleeding event was analyzed using the Kaplan–Meier plot with the Mantel–Cox log-rank test to assess for difference between DOAC and warfarin groups. Cox proportional hazards model on time to major bleeding event was performed. This model considered DOAC use versus warfarin and included potential confounders identified by prior research. Calendar year of anticoagulation initiation was also included to account for unmeasured changes in practice and patient care over time. The proportional hazards assumption was tested using Schoenfeld residuals in the final model using chi-

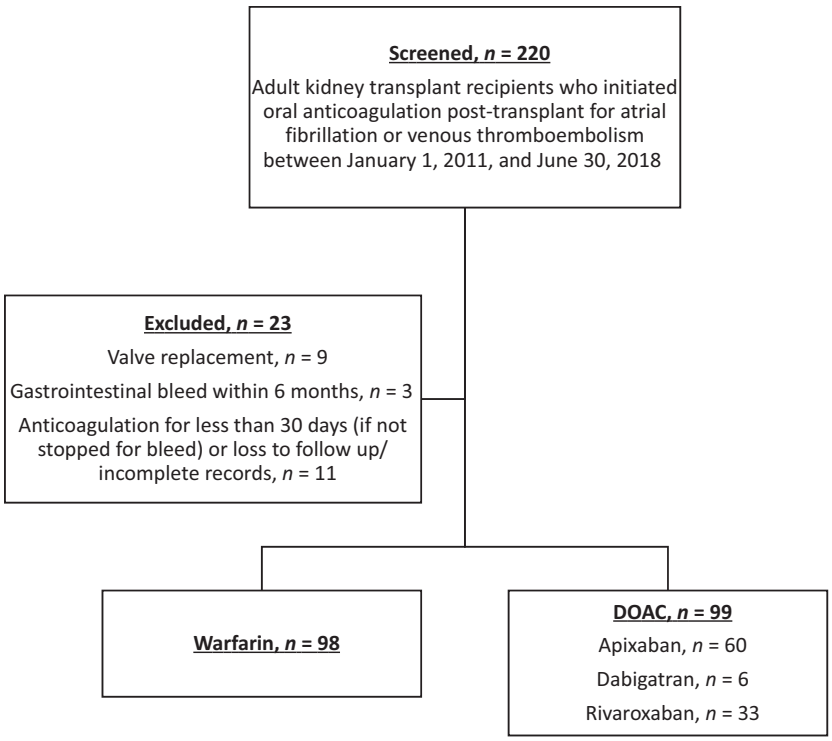


**Figure 1** Study design.



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square test [14,15]. In a sensitivity analysis, we ran the same model excluding those with prior bleeding episodes. Results were considered significant with a two-sided $P$-value <0.05. Statistical analyses were performed using IBM SPSS version 24 (IBM Corp., Armonk, NY, USA) and R version 3.6.1 [16].

## Results

### Patients

A total of 197 kidney transplant recipients were included in this study (Fig. 1). Patients were initiated on warfarin or DOAC therapy at a median of 6.5 (IQR 2.6–11.2) years post-transplant and followed for a median of 12.3 (IQR 5.2–27.5) months on anticoagulation. Despite that no formal matching was done, the two groups had similar baseline demographics and clinical characteristics (Table 1). The only differences were Hgb, concomitant antiplatelet use at time of anticoagulation initiation, and calendar year of anticoagulation initiation.

### Safety and efficacy

There was no difference in major bleeding events between patients on DOACs versus warfarin in the time-to-event analysis (Fig. 2, Mantel–Cox $P = 0.15$). The rates of major bleeding were 7.2% per year with DOACs vs. 11.4% per year with warfarin. Major bleeding events occurred at a median of 12.0 (IQR 1.3–30.8) months after initiation of anticoagulation. There was no difference in classification of major bleeding (Table 2), but numerically more warfarin patients, who had major bleeding event, experienced bleeding at a critical site or organ (38% vs. 11%). Approximately 10% of patients in both groups had a procedure within 5 days prior to the major bleeding event. Twenty-one patients had a major bleeding event on warfarin therapy. Of these patients, 38% had a supratherapeutic international normalized ratio (INR) at the time of bleeding event (defined as an INR greater than 3). The median INR at the time of bleeding event was 2.5 (range 1.1–9.6).

The rates of composite bleeding were 19.4% per year with DOAC vs. 20.8% per year with warfarin, and they were not statistically different between groups in the time-to-event analysis. New VTE occurred in 3.1% vs. 2.0% ($P = 0.50$) and stroke occurred in 5.1% vs. 1.0% ($P = 0.13$) of warfarin and DOAC patients, respectively. The median time to VTE or stroke was 371 days (IQR 159–813 days). The shortest onset to VTE was 10 days for a patient taking apixaban. This patient was on a CYP3A4 inducer, which may have led to subtherapeutic apixaban levels. There was no difference between groups in the number of patients that died during follow-up (9.2% with warfarin vs. 7.1% with DOAC, $P = 0.59$). None of the DOAC patients with a VTE or stroke were underdosed for their level of kidney function.

### Comparison of different DOAC agents

There was no statistical difference in the safety or efficacy outcomes when comparing the three DOACs (Table 3). There were only six patients on dabigatran and no major bleeding events occurred on this agent. Interestingly, 6.7% of patients on apixaban experienced a major bleeding event versus 15.2% on rivaroxaban ($P = 0.19$). When apixaban alone was compared to warfarin there was a lower incidence of major bleeding (6.7% vs. 21.4%, $P = 0.014$) and a trend toward lower composite bleeding (21.7% vs. 34.7%, $P = 0.08$). Similarly, when apixaban was compared to all other agents (warfarin, dabigatran, and rivaroxaban), there was a lower incidence of major bleeding (6.7% vs. 19.0%, $P = 0.027$), but no difference in composite bleeding (21.7% vs. 32.8%, $P = 0.11$). None of the patients that experienced a major bleeding event were considered overdosed based on their renal function at the time of the bleed. There were no differences between any of the agents regarding stroke and VTE events during anticoagulation therapy.

### Cox regression

Multivariable Cox regression analysis for associations with time to major bleeding events is presented in Table 4. In the model, safety of DOAC use was not associated with an increased risk of bleeding when compared to warfarin (HR 0.73, CI 0.27–1.95; $P = 0.529$) even after controlling for the potential confounders. Prior bleeding events (HR 3.86, CI 1.41–10.57; $P = 0.009$) and having a deceased donor (HR 2.74, CI 1.16–6.45, $P = 0.021$) were significant risk factors for major bleeding. Higher baseline Hgb levels were protective of bleeding (HR 0.66, CI 0.54–0.82; $P < 0.001$). The Schoenfeld test for models meeting proportional hazards showed agreement with hypotheses ($\chi^2 = 20.7$, $P = 0.079$). In our sensitivity analysis looking at those without prior bleeding events, DOAC use was not more or less protective than warfarin for major bleeding events (HR 0.83, CI 0.26–2.67; $P = 0.759$). Again,

**Table 1.** Baseline demographics and clinical characteristics.

| Outcome | All (*n* = 197) | Warfarin (*n* = 98) | DOAC (*n* = 99) | *P*-value |
|---|---|---|---|---|
| Age, median (IQR) | 62.2 (55.4–68.9) | 62.3 (54.4–68.4) | 62.0 (56.5–70.3) | 0.52 |
| Sex, *n* (%) | | | | |
| Male | 133 (68) | 62 (63) | 71 (72) | 0.21 |
| Female | 64 (33) | 36 (37) | 28 (28) | |
| Race, *n* (%) | | | | |
| Caucasian | 146 (74) | 69 (70) | 77 (78) | 0.15 |
| Black | 38 (19) | 24 (25) | 14 (37) | |
| Other | 13 (7) | 5 (39) | 8 (8) | |
| Reason for transplant, *n* (%) | | | | |
| DM (type I or II) | 62 (32) | 31 (32) | 31 (31) | 0.81 |
| HTN | 28 (14) | 14 (14) | 14 (14) | |
| Polycystic kidney disease | 26 (13) | 13 (13) | 13 (13) | |
| Glomerulonephritis | 16 (8) | 11 (11) | 5 (5) | |
| IgA nephropathy | 15 (8) | 6 (6) | 9 (9) | |
| FSGS | 11 (6) | 6 (6) | 5 (5) | |
| SLE | 6 (3) | 3 (3) | 3 (3) | |
| Other/unknown | 33 (17) | 14 (14) | 19 (19) | |
| Donor type, *n* (%) | | | | |
| Deceased donor | 104 (53) | 57 (58) | 47 (48) | 0.13 |
| Living donor | 93 (47) | 41 (42) | 52 (53) | |
| Calcineurin inhibitor, *n* (%) | | | | |
| Tacrolimus | 151 (77) | 74 (76) | 77 (78) | 0.87 |
| Cyclosporine | 41 (21) | 21 (21) | 20 (20) | |
| Time from transplant to initiation of anticoagulation, years, median (IQR) | 6.5 (2.6–11.2) | 6.4 (1.6–12.5) | 6.5 (2.8–10.8) | 0.98 |
| Follow-up, months, median (IQR) | 12.3 (5.2–27.5) | 13.1 (5.0–36.8) | 11.0 (5.3–18.5) | 0.15 |
| Indication, *n* (%) | | | | |
| VTE | 103 (52) | 57 (58) | 46 (47) | 0.10 |
| Atrial fibrillation | 94 (48) | 41 (42) | 53 (54) | |
| VTE index event, *n* (%) | | | | |
| Deep vein thrombosis | 79 (48) | 43 (42) | 36 (36) | 0.41 |
| Pulmonary embolism | 22 (40) | 13 (13) | 9 (9) | |
| Both | 2 (11) | 1 (1) | 1 (1) | |
| CHA2DS2-VASc*, mean ± SD | 3.5 ± 1.6 | 3.5 ± 1.4 | 3.5 ± 1.7 | 0.27 |
| ATRIA*, mean ± SD | 3.4 ± 2.0 | 3.6 ± 2.1 | 3.2 ± 1.9 | 0.21 |
| Pertinent comorbidities, *n* (%) | | | | |
| Prior VTE event | 33 (17) | 15 (15) | 18 (18) | 0.59 |
| Prior bleed | 25 (13) | 11 (11) | 14 (14) | 0.52 |
| Stroke | 19 (10) | 10 (10) | 9 (9) | 0.79 |
| Year anticoagulation started | | | | |
| 2011–2013 | 33 (17) | 25 (26) | 8 (8) | <0.001 |
| 2014 | 26 (13) | 16 (16) | 10 (10) | |
| 2015 | 34 (17) | 23 (23) | 11 (11) | |
| 2016 | 35 (18) | 13 (13) | 22 (22) | |
| 2017 | 33 (17) | 17 (17) | 16 (16) | |
| 2018 | 36 (18) | 4 (4) | 32 (32) | |

having a deceased donor was a hazard (HR 2.77, CI 1.07–7.13; $P = 0.035$) and higher baseline Hgb levels were protective (HR 0.068, CI 0.54–0.86; $P = 0.001$). Additionally, concomitant antiplatelet use was protective (HR 0.35, CI 0.13–0.96; $P = 0.042$).

## Discussion

In this single-center retrospective study, we evaluated 197 kidney transplant recipients who were either on DOAC or warfarin therapy for the treatment of VTE or



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**Table 1.** Continued.

| Outcome | All (*n* = 197) | Warfarin (*n* = 98) | DOAC (*n* = 99) | *P*-value |
|---|---|---|---|---|
| Concomitant antiplatelet use, *n* (%) | 96 (49) | 56 (57) | 40 (40) | 0.02 |
| Drug interactions present, *n* (%) | | | | |
| CYP3A4 and/or P-gp inhibitors | | | | |
| Diltiazem | 15 (8) | 5 (5) | 10 (10) | 0.29 |
| Amiodarone | 6 (3) | 2 (2) | 4 (4) | |
| Itraconazole | 2 (1) | 2 (2) | 0 (0) | |
| Verapamil | 1 (0.5) | 1 (1.0) | 0 (0) | |
| Voriconazole | 1 (0.5) | 0 (0) | 1 (1.0) | |
| Diltiazem and amiodarone | 2 (1.0) | 0 (0) | 2 (2.0) | |
| CYP3A4 inducer | | | | |
| Carbamazepine | 1 (0.5) | 0 (0) | 1 (1.0) | |
| eGFR by MDRD-4, ml/min/1.73 $m^2$, median (IQR) | 52.4 (41.0–64.4) | 50.0 (35.3–63.1) | 54.5 (43.0–64.8) | 0.68 |
| eGFR <30 ml/min/1.73 $m^2$ | 22 (11.2) | 15 (15.3) | 7 (7.1) | 0.067 |
| Hgb, g/dl, mean ± SD | 12 ± 2 | 11.5 ± 2.1 | 12.5 ± 2.1 | 0.001 |

ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CYP, cytochrome P-450; DM, diabetes mellitus; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; IQR, interquartile range; MDRD, modification of diet in renal disease study equation; P-gp, P-glycoprotein; SD, standard deviation; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

*For atrial fibrillation patients only.

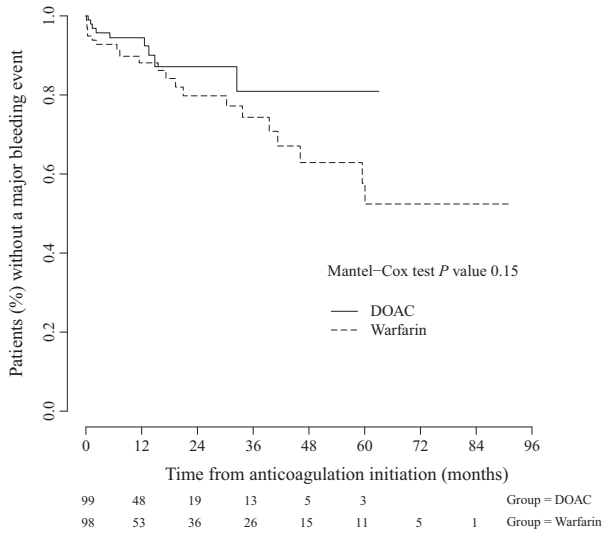


**Figure 2** Kaplan–Meier plot for major bleeding event.

primary prevention of thromboembolic events associated with nonvalvular atrial fibrillation. The groups had similar baseline characteristics, with the exception of baseline Hgb, concomitant antiplatelet use, and calendar year when anticoagulation was started. Warfarin was the predominantly used anticoagulant in the beginning of the study period. Practice shifted from warfarin use to DOAC use after 2013. This trend is consistent with national prescribing data among the general population and among patients with kidney disease [17,18].

In our study cohort, the overall incidence of composite bleeding was 29% with 15% of patients experiencing a major bleed. The rates of major bleeding and composite bleeding in DOAC patients were 7.2% and 19.4% per year, respectively. These rates are substantially higher than those reported in the clinical trials of DOAC therapy in nontransplant populations (major bleed 0.6–3.6% and any bleed 5.6–18.2%) [19-24]. With warfarin therapy, the rates were even higher for both major and composite bleeding (11.4% and 20.8% per year, respectively); however, they were not statistically different from DOAC group. An earlier meta-analysis of five randomized controlled trials for the treatment of VTE found that DOACs significantly reduced risk of major bleeding compared with warfarin (RR 0.60, 95% CI 0.41–0.88) [25]. A more recent meta-analysis of 13 randomized controlled trials for stroke or systemic embolism prevention in patients with atrial fibrillation also found a significantly lower risk of major bleeding with DOACs (OR 0.78, 95% CI 0.73–0.84) [26].

It is possible that the higher incidence of bleeding seen in our study is due to the ability to capture bleeding events utilizing a search feature or the ability to see admissions for bleeding at outside institutions in the electronic medical record. Additionally, surgical or procedure-related bleeding was possible in this study. Procedures that preceded bleeding events were captured. Because of the lack of transplant specific definition for

**Table 2.** Major bleeding.

| Outcome | All (*n* = 30) | Warfarin (*n* = 21) | DOAC (*n* = 9) | *P*-value |
|---|---|---|---|---|
| Classification, *n* (%) | | | | |
| Bleeding at critical site/organ | 9 (30.0) | 8 (38.1) | 1 (11.1) | 0.13 |
| pRBC ≥2 units | 12 (40.0) | 7 (33.3) | 5 (55.5) | |
| Decrease in Hgb ≥2 g/dl | 9 (30.0) | 6 (28.6) | 3 (33) | |
| Site of bleeding, *n* (%) | | | | |
| Gastrointestinal | 12 (40.0) | 8 (38.1) | 4 (44.4) | 0.13 |
| Hematuria | 2 (6.7) | 0 (0) | 2 (22.2) | |
| Intracranial | 1 (3.3) | 1 (4.8) | 0 (0) | |
| Musculoskeletal | 3 (10.0) | 2 (9.5) | 1 (11.1) | |
| Pericardial | 1 (3.3) | 0 (0) | 1 (11.1) | |
| Retroperitoneal | 6 (20) | 6 (28.6) | 0 (0) | |
| Eye/ocular | 1 (3.3) | 1 (4.8) | 0 (0) | |
| Other/unknown | 4 (13.3) | 3 (14.3) | 1 (11.1) | |
| Procedure within 5 days, *n* (%) | 3 (10.0) | 2 (9.5) | 1 (11.1) | 0.67 |
| Hgb at bleeding, g/dl, mean ± SD | 7.7 ± 2.0 | 8.0 ± 2.1 | 7.2 ± 1.8 | 0.31 |
| Indication, *n* (%) | | | | |
| Atrial fibrillation | 20 (66.7) | 13 (61.9) | 7 (77.8) | 0.40 |
| VTE | 10 (33.3) | 8 (38.1) | 2 (22.2) | |
| Renal function | | | | |
| At baseline | | | | |
| eGFR, ml/min/1.73 $m^2$, median (IQR) | 50.1 (42.2–55.9) | 46.4 (37.2–58.1) | 53.3 (47.3–60.5) | 0.20 |
| At bleed | | | | |
| Dialysis, *n* (%) | 3 (10.0) | 3 (14.3) | 0 (0) | 0.53 |
| eGFR, ml/min/1.73 $m^2$, median (IQR) | 42.7 (30.4–50.9) | 42.0 (29.2–53.2) | 45.0 (34.9–53.3) | 0.57 |

DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; IQR, interquartile range; pRBC, packed red blood cells; SD, standard deviation; VTE, venous thromboembolism.

**Table 3.** Bleeding and thromboembolic outcomes.

| Outcome, *n* (%) | Warfarin (*n* = 98) | All DOAC (*n* = 99) | Apixaban (*n* = 60) | Dabigatran (*n* = 6) | Rivaroxaban (*n* = 33) |
|---|---|---|---|---|---|
| Composite bleed | 34 (34.7) | 24 (24.2) | 13 (21.7) | 2 (33.3) | 9 (27.3) |
| Major bleed | 21 (21.4) | 9 (9.1) | 4 (6.7)* | 0 (0%) | 5 (15.2) |
| CRNMB | 14 (14.3) | 16 (16.2) | 9 (15) | 2 (33.3) | 5 (15.2) |
| VTE | 3 (3.1) | 2 (2.0) | 1 (1.7) | 0 (0) | 1 (3.0) |
| Stroke | 5 (5.1) | 1 (1.0) | 1 (1.7) | 0 (0) | 0 (0) |

CRNMB, clinically relevant nonmajor bleeding; DOAC, direct oral anticoagulant; VTE, venous thromboembolism.

*$P$ = 0.014 compared with the major bleeding incidence of warfarin (21.4%); $P$ = 0.027 compared with the major bleeding incidence of all the other agents (19.0%).

major bleeding, we decided to use the nonsurgical major bleeding definition because the median time from transplant was 6.5 years. The bleeding definition will need to be better defined in a kidney transplant population in a prospective study.

In our study, more warfarin patients had major bleeding at a critical site or organ (38% vs. 11%). This was consistent with findings in nontransplant populations. The meta-analysis of VTE trials found a lower risk of nonfatal bleeding at a critical site (RR 0.38, 95% CI 0.23–0.62) and the meta-analysis of atrial fibrillation trials found a lower risk for intracranial hemorrhage with DOACs than warfarin (RR 0.50, 95% CI 0.42–0.59) [25,26].

There is a limited amount of data examining DOAC use in solid organ transplant recipients as most of the reports are in abstracts or conference proceedings (Table 5) [27-44]. The bleeding incidences in our DOAC group were within the previously reported ranges of composite bleeding (6–37%) and major



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**Table 4.** Multivariable cox regression: risk for major bleeding.

| Variable | HR (95% CI) | *P*-value |
|---|---|---|
| DOAC use | 0.73 (0.27–1.95) | 0.529 |
| Age (years) | 1.00 (0.96–1.05) | 0.835 |
| Prior bleed | **3.86 (1.41–10.57)** | **0.009** |
| Concomitant antiplatelet use | 0.49 (0.21–1.14) | 0.097 |
| eGFR <30 ml/min/1.73 $m^2$ | 0.67 (0.21–2.10) | 0.488 |
| Atrial fibrillation | 2.11 (0.94–4.77) | 0.071 |
| Deceased donor transplant | **2.74 (1.16–6.45)** | **0.021** |
| Hgb at initiation (g/dl) | **0.66 (0.54–0.82)** | **<0.001** |
| Anticoagulation start 2014 vs. 2011–2013 | 1.07 (0.23–4.93) | 0.934 |
| Anticoagulation start 2015 vs. 2011–2013 | 2.18 (0.63–7.49) | 0.217 |
| Anticoagulation start 2016 vs. 2011–2013 | 1.44 (0.35–5.82) | 0.612 |
| Anticoagulation start 2017 vs. 2011–2013 | 0.99 (0.19–5.32) | 0.994 |
| Anticoagulation start 2018 vs. 2011–2013 | 2.55 (0.40–16.30) | 0.321 |

CI, confidence interval; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HR, hazard ratio.

Bolded variables are statistically significant with $P < 0.05$.

bleeding (0–23%). Our study does have a numerically higher incidence of bleeding when compared to some of the other studies which may be related to sample size, duration of follow-up, and access to electronic medical records from outside institutions. To our knowledge, this is the largest study to date that compared DOACs to warfarin in kidney transplant recipients.

In addition to the sparse data of DOAC use in transplant recipients, there is even less data comparing DOAC users to warfarin users among transplant recipients. Comparative studies are limited to abstracts only. Santeusanio *et al.* [39] found a higher incidence of clinically significant bleeding with the warfarin group compared to the DOAC group in liver transplant recipients (50% vs. 15%, $P = 0.01$). When Tremblay-Gravel *et al.* [42] compared warfarin to DOACs in heart transplant recipients, they found an increased risk of bleeding with warfarin (OR 4.55, 95% CI 1.2–16.2). However, it should be noted that baseline renal function was significantly worse in the warfarin group with 43% of warfarin patients and 5% of DOAC patients on dialysis. Hazelcorn *et al.* [31] found no difference in major bleeding between warfarin and DOAC groups (5% vs. 11%, $P = 0.42$) in various organ transplant recipients, but the study was likely underpowered to detect a difference. Although our study did not find a difference in major bleeding incidence between all DOACs and warfarin, we did find a lower incidence of major bleeding with apixaban compared to warfarin (6.7% vs. 21.4%, $P = 0.014$) in kidney transplant recipients. Although there is heterogeneity among these studies, they do indicate a trend toward lower major bleeding risk with DOACs compared to warfarin in solid organ transplant recipients.

It is possible that the lower event rates seen with DOAC agents are fueled by the low number of bleeding events for patients on apixaban therapy. In our study, there was a lower incidence of major bleeding when apixaban was compared to warfarin alone and when compared to a composite of warfarin, dabigatran, and rivaroxaban. We found no difference in composite bleeding event when apixaban was compared to any other agents. Pasley *et al.* [38]. compared heart and lung transplant recipients that were using apixaban to a group of nonapixaban DOACs. They found no difference in major (0% vs. 1%) or composite bleeding (10% vs. 15%, $P = 0.75$). Interestingly, McMurry *et al.* [36]. found a higher incidence of composite bleeding events when rivaroxaban was compared to apixaban among all solid organ transplant recipients (12% vs. 2%, $P = 0.006$). In our study, rivaroxaban compared to other DOACs was associated with a numerically higher incidence of major bleeding, but this was not statistically significant (15.2% vs. 6.7%, $P = 0.12$). Solid organ transplant recipients often have risk factors present that increase their risk for bleeding. Specifically, transplant recipients are at risk for developing chronic renal failure and thus it is important to consider renal elimination of DOAC agents. Of the DOACs currently approved for the treatment of VTE and prevention of stroke, apixaban relies the least on renal clearance (27%) [11-13]. This is potentially why there appears to be a lower incidence of bleeding with apixaban.

**Table 5.** Current literature examining direct oral anticoagulants in solid organ transplant recipients [27-44].

| Study | *N* (for DOAC) | Organ | DOAC | CNI (% tacrolimus) | Major bleed (%) | Any bleed (%) | VTE/stroke (%) | Follow-up (months) | Dose adjustment (%) | Inappropriate adjustment* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Present study | 98 | Kidney | Any | 78% | 9% | 24% | 3% | 12 (median) | 19% | 13% |
| Amborsi | 11 | Heart | R | 27% | 10% | – | 0% | – | 100% | – |
| Bellam | 23 | Heart | R or A | 100% | 0% | 0% | 0% | 5 (median) | 13% | – |
| Brown | 162 | Any | A | | 3% | 17% | 4% | 6 (NS) | – | – |
| Do | 52 | Kidney | A | – | 4% | 12% | 4% | – | – | 10% |
| Hazelcorn | 37 | Any | R or A | 97% | 11% | – | – | – | 49% | 8% |
| Kim | 7 | Heart | D or R | 100% | 0% | 14% | 0% | 5 (median) | 14% | – |
| Leon | 33 | Kidney | Any | – | 0% | 12% | 0% | 13 (median) | – | – |
| Lichvar | 37 | Heart or Lung | Any | 76% | 3% | 19% | 5% | 3 (median) | 60% | - |
| Loosier | 22 | Kidney | A | – | 0% | 0% | 5% | 12 (NS) | – | 32% |
| McMurry | 172 | Any | R or A | – | – | 6% | 1% | – | – | 28% |
| Pasley | 38 | Heart or Lung | Any | – | 0% | 16% | 21% | – | – | 68% |
| Pasley | 109 | Heart or Lung | Any | – | 1% | 14% | 9% | – | – | 51% |
| Santeusansio | 27 | Liver | Any | – | – | 15% | 15% | 12 (median) | – | – |
| Shaikh | 62 | Kidney | Any | – | 23% | 37% | 0% | 9 (median) | 35% | 18% |
| Shuster | 27 | Heart | Any | 93% | 9% | – | – | – | – | – |
| Tremblay-Gravel | 62 | Heart | Any | – | – | – | – | – | – | – |
| Vanhove | 39 | Any | R or A | 74% | 0% | 5% | – | 34 (mean) | – | – |
| Wanhoff | 9 | Liver | R | 44% | – | 33% | 0% | 11 (median) | 38% | – |

A, apixaban; CNI, calcineurin inhibitor; D, dabigatran; DOAC, direct oral anticoagulant; NS, not specified; R, rivaroxaban; VTE, venous thromboembolism.

*Based on study definitions.

There is some information suggesting a potential interaction between DOACs and cyclosporine resulting in increases of DOAC concentrations through inhibition of P-gp [8]. However, this interaction is not significant enough to require empiric dose adjustments [11-13]. Interestingly, DOACs are often dose adjusted in solid organ transplant recipients whether or not it is supported by the approved labeling (Table 5).

Solid organ transplant recipients often undergo surveillance or for-cause biopsy. Anticoagulation should be held prior to organ biopsy to reduce the risk for bleeding events. In our study, there was only one bleed (CRNMB) following organ biopsy in a patient on apixaban. Despite holding apixaban for one week prior to biopsy, the patient developed hematuria postbiopsy leading to hospitalization. Hazelcorn *et al.* [31] found that 50% of major bleeding events occurred after organ biopsy. However, it is not clear how long anticoagulation was held prior to biopsy. Another study described that protocol biopsies were not performed in 50% of patients because of DOAC use [28]. Prior studies have shown low rates of postbiopsy bleeding among the transplant population. However, many surveillance biopsies were canceled in these studies indicating that providers may be uncomfortable performing biopsies for patients on DOAC.

In our Cox regression model, we accounted for differences in baseline characteristics and found no association between DOAC use and major bleeding (HR 0.73, 95% CI 0.27–1.95; $P = 0.53$). Prior bleeding events and having a deceased donor were risk factors for major bleeding. It is possible that deceased donor is a risk factor for bleeding because of the increased time spent on dialysis compared with living donor kidney transplant recipients. Patients on dialysis are known to have platelet dysfunction and are at increased risk of gastrointestinal bleeding because of angiodysplasias [45,46]. After transplant, it can take up to 2 years for platelet function to normalize [45]. The combination of these factors is one potential reason that deceased donor transplant recipients may be at a higher risk for bleeding. However, it is important to note that the median time from transplant in our study was 6.5 years and it is unlikely that platelet dysfunction would persist in those patients several years from transplant.

The incidence of VTE and stroke in this study is similar to what has been reported in previous publications of DOAC use in transplant recipients (Table 5). In fact, the incidences of VTE and stroke on DOACs in our study are substantially lower than other studies that have reported inappropriate DOAC dose adjustments in 68% of patients (3% vs. 21%) [37].

As a retrospective single-center cohort study, there are several limitations to this study. Data were dependent on documentation in the medical record, which may have resulted in underreporting of safety or efficacy outcomes. If the patient presented to a local hospital with a bleeding or thrombotic event, it is possible that this information could have been missed. Because of the retrospective nature, we were unable to capture fluctuations in renal function and INR, changes in antiplatelet therapy, drug–drug interactions, or adherence to anticoagulation throughout the entire follow-up period. Although our study is one of the largest to date looking at DOAC use in transplant recipients, the sample size is small making it difficult to detect a statistical difference in all bleeding outcomes. There are several strengths to be noted including the long follow-up period and that DOAC use was compared with the historic standard of care, warfarin. Additionally, both groups were similar in regard to baseline characteristics with the exception of lower Hgb and more frequent concomitant antiplatelet use in the warfarin group.

Direct-acting oral anticoagulant therapy is often utilized as an alternative to warfarin in solid organ transplant recipients. Based on the results of our study, DOACs had an acceptable safety and efficacy profile compared with warfarin for the management of VTE and prevention of stroke following nonvalvular atrial fibrillation in kidney transplant recipients. However, further studies are warranted to demonstrate that DOACs are safe and effective alternatives to warfarin in kidney transplant recipients.

## Authorship

AB, SS, AN, LC, MS and JP: contributed to the design of the study. AB, SS, LC, KM and JP: contributed to obtaining data. AB, AN, VM and JP: contributed to data analysis. AB, SS, AN, LC, MS, JP, KM and VM: contributed to writing and review of the article.

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