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Management of Atrial Fibrillation after Kidney Transplant: Do We Need a New Metric?

Maria V. Fonseca Bauza [1, †], Aimee H. Dubin [2, †], Chris B. Agala [3], Alexander H. Toledo [4], Kristen R. Szempruch [5], David A. Gerber [6], Pablo Serrano Rodriguez [7, *]

1. School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; E-Mail: maria_fonseca@med.unc.edu
2. School of Medicine, University of Campbell, Lillington, NC, USA; E-Mail: ahdubin0206@email.campbell.edu
3. Department of Surgery, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; E-Mail: chris_agala@med.unc.edu
4. Division of Abdominal Transplant Surgery, University of North Carolina, Chapel Hill, NC, USA; E-Mail: alexander_toledo@med.unc.edu
5. Department of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; E-Mail: kristen.szempruch@unchealth.unc.edu
6. Department of Surgery, University of Cincinnati, Cincinnati, OH, USA; E-Mail: gerberdd@ucmail.uc.edu
7. Division of Abdominal Transplant Surgery, George Washington University, Washington, D.C., USA; E-Mail: pserrano@mfa.gwu.edu

† These authors contributed equally to this work.

* **Correspondence:** Pablo Serrano Rodriguez; E-Mail: pserrano@mfa.gwu.edu

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Abstract

To evaluate the bleeding risk associated with anticoagulation (AC) in kidney transplant patients with post-operative atrial fibrillation (AF). We conducted a retrospective analysis of all adult kidney transplant recipients performed from October 2012 to February 2019 at our

institution, the University of North Carolina at Chapel Hill, which accounted for 428 transplants. Variables assessed included AF occurrence, AC use, bleeding complications, stroke and bleeding risk stratification in AF (determined using CHA_2DS_2-VASc and HAS-BLED scores respectively), and renal function. Adjusted odds ratios, relative risk and linear estimates and their 95% confidence intervals and corresponding p-values were estimated to identify risk factors of interest using multivariate logistic regression and generalized linear and linear models. Of the 428 kidney transplant patients analyzed, 6.8% (n = 29) developed AF, and 51.7% (n = 15) of these patients received AC. Among those on AC, 73.3% (n = 11) experienced bleeding complications, and 36.4% (n = 4) required medical intervention. AC use was associated with higher odds of post-transplant interventions (OR = 4.62, 95% CI: 1.63-13.13, p = 0.0041), including a return to surgery (OR = 7.34, 95% CI: 2.32-23.25, p = 0.0007). Higher HAS-BLED scores correlated with increased odds of intervention (OR = 1.61, 95% CI: 1.1-2.36, p = 0.0143). Patients on AC also had higher creatinine levels at discharge and increased odds of delayed graft function (OR = 3.27, 95% CI: 1.45-7.35, p = 0.0042), longer hospital stays, and increased readmission rates. No patients developed a stroke during follow-up. Kidney transplant recipients with AF who receive AC face substantial bleeding risks. While CHA_2DS_2-VASc and HAS-BLED scores are valuable for assessing patients with AF, they may be inadequate for managing AF in post-kidney transplant or post-surgical settings. This study is the first to evaluate the risk of AC and early post-operative bleeding in kidney transplant recipients with new-onset AF.

Keywords
Atrial fibrillation; kidney transplant; anticoagulation

1. Introduction

Atrial fibrillation (AF) is the most common and clinically significant cardiac arrhythmia, occurring in 2% of the general population and increases the risk of stroke fivefold [1-3]. However, chronic kidney disease (CKD) patients have a higher incidence of AF at 19-24% and an increased risk of stroke in patients following a kidney transplant [2]. The leading cause of death following kidney transplant is cardiovascular disease, which is responsible for 30-50% of the deaths within one month post-transplant. Over 50% of cardiovascular-related deaths after a kidney transplant are sudden and presumed to be secondary to cardiac arrhythmia and cardiac arrest [2, 4, 5].

Currently, the CHA_2DS_2-VASc score, which accounts for congestive heart failure, hypertension, age 65-74 years, diabetes mellitus, female sex, vascular disease (1 point each), and age ≥75 years or stroke/TIA (2 points each), with scores ranging from 0 to 9 and the HAS-BLED score, which evaluates hypertension, renal disease, liver disease, stroke history, bleeding history or predisposition, labile international normalized ratio [INR], age >65 years, medication usage predisposing to bleeding, and alcohol use (1 point each), also with scores ranging from 0 to 9, are the gold standard to determine stroke and bleeding risks, respectively, in AF patients [6]. CHA_2DS_2-VASc calculates stroke risk for AF patients, influencing the decision to administer anticoagulation (AC) post-transplant and HAS-BLED assesses bleeding risk for AF patients on AC. Higher CHA_2DS_2-VASc scores guide AC use, while

elevated HAS-BLED scores indicate bleeding risk, and is used to assess discontinuing AC use. Despite these two stratification tools, there are no specific guidelines for the management of AF in non-cardiac surgical patients including unique patient populations (e.g., kidney transplant recipients). It is crucial to highlight that these scoring systems are primarily designed for patients who have not undergone surgery, as their focus is on estimating the risk of stroke and bleeding within a one-year timeframe [7, 8]. Importantly, these assessments may not comprehensively account for additional risks associated with surgical procedures, which could potentially elevate the risk of bleeding.

In patients with CKD, there is an increased likelihood of both major hemorrhagic and thromboembolic events [9-12]. The reasons for this complex coagulopathy include vascular defects and clotting disturbances, showing these patients can be both hypo- and hypercoagulable. As renal dysfunction increases the risk of bleeding, the most common early surgical complication after kidney transplant is bleeding, occurring in up to 8% of patients while the risk of thrombosis is approximately 3% [13-15]. Despite this, most CKD and end-stage renal disease (ESRD) patients are excluded or underrepresented in studies involving arrhythmia treatments [16, 17]. As a result, the current therapeutic approach in patients with ESRD and AF is identical to the treatment of AF in the general population, centered around the administration of blood thinners to mitigate the risk of stroke. AC are commonly used to reduce thrombotic events in AF patients, in turn, increasing the risk of early postoperative bleeding. There are no randomized studies evaluating AC in kidney transplant recipients [2].

The CHA_2DS_2-VASc and HAS-BLED scores have also been shown to underestimate scores for patients with renal impairment, specifically because these patients tend to have higher postoperative AF risk at a significantly younger age, as well as higher incidence of high blood pressure, vascular disease and diabetes [9, 18]. As a result, additional data are required to elucidate optimal strategies for preserving transplant graft function in patients with AF, while concurrently mitigating the risk for thromboembolic events or hemorrhage in the early post-operative period. The study's objective is to assess the risk of bleeding after the start of AC in kidney transplant recipients with new onset AF.

2. Methods

We performed a retrospective analysis of all adult kidney transplant recipients at our institution, the University of North Carolina at Chapel Hill, from October 1, 2012 to February 1, 2019.

2.1 Ethics Statement

The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board of the University of North Carolina at Chapel Hill on 1/11/2019 (18-3301). Written informed consent has been obtained from patients to publish this paper. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19] and was reviewed and approved by the Institutional Review Board. It included both living and deceased donors, excluding multivisceral and pediatric transplants. They were managed with standard immunosuppression, induction with Alemtuzumab and maintenance with tacrolimus and mycofenolic acid with a rapid steroid taper.

3. Baseline Variables

Baseline variables were abstracted retrospectively from patient medical records. These variables included demographic data (such as sex, age, race, and ethnicity), clinical characteristics (such as presence of vascular disease, diabetes mellitus, and BMI), and perioperative factors (such as the need for anticoagulation and LOS). The risk stratification of stroke and bleeding in AF (determined using CHA_2DS_2-VASc and HAS-BLED scores respectively) were calculated at the time of transplant. We evaluated the development of AF within the first 30 days after transplant, the initiation of AC at that time, and the occurrence of bleeding following the start of AC. Only kidney transplant recipients who were administered therapeutic AC were evaluated in this study. This encompassed all forms of AC, including warfarin, heparin and direct oral anticoagulants. AC used solely for deep vein thrombosis prophylaxis was not considered in this analysis.

3.1 Outcomes

The primary outcome was incidence of bleeding after the start of anticoagulation (defined as a decrease in hemoglobin by more than 2 g/dl within 30 days post-transplant). Secondary outcomes included requirement of an intervention (operation, blood transfusion, or additional medical observation), readmission within 30 days post-procedure, delayed graft function (defined as the necessity for dialysis within one week post-transplant), index length of stay, and renal function (assessed by peak serum creatinine during the index admission and at the time of discharge). The intervention of additional medical observation consisted of repeat complete blood counts with close monitoring for potential bleed. Additionally, kidney transplant patients must follow up twice a week in the first month after discharge, once a week in the second month, and every other week thereafter for six months. All patients adhered to this standard of follow-up care.

3.2 Covariates

The key independent variable was whether a patient had atrial fibrillation. Other covariates included sex, age, race and ethnicity, use of anticoagulant, vascular disease, diabetes mellitus, body mass index (BMI), and length of stay (LOS). CHA_2DS_2-VASc and HAS-BLED defined above.

3.3 Statistical Analysis

We used frequencies, percentages, means, standard deviations, medians and interquartile ranges to describe patient characteristics by patients that had AF (AFIB) vs patients that did not (no AFIB) groups. We compared the two groups using the chi square test and Wilcoxon rank sum test after normality tests including visual inspection of histograms and Shapiro-Wilk test showed the data were not normally distribution. We used multivariate binary logistic regression to assess the associations between the risk factors and binary outcomes including readmission, bleeding, dialysis, and any intervention, such as surgery, Poisson regression for count outcome - for length of stay and linear regression for continuous outcomes - creatinine before discharge and highest creatinine values. Adjusted odds ratios (OR), relative risk and linear estimates and their 95% confidence intervals (CI) and p-values are reported for the associations between the risk factors and the outcomes. All analyses were conducted using the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) [20].

4. Results

In our study, we enrolled 428 patients during our study period, with 59.1% (n = 253/428) identifying as male at birth. Our cohort consisted of 42.3% (n = 181/428) Caucasian and 44.6% (n = 191/428) African American patients. Among these, 4.4% (n = 19/428) had vascular disease, 18.9% (n = 81/428) had diabetes mellitus, and approximately 20.8% (n = 89/428) required readmission within 30 days after discharge post-transplantation. The average age of patients at the time of transplant was 49.8 years, with a mean BMI of 28.4. The mean length of stay was 6.7 days, and the follow-up period was six months (Table 1).

Table 1 Baseline characteristic of study participants by atrial fibrillation status, n = 428.

Characteristic	Categories	Overall, n = 428		No atrial fibrillation n = 399		Atrial fibrillation, n = 29		p-value*
		Frequency or Mean	*% or Standard deviation*	Frequency or Mean	*% or Standard deviation*	Frequency or Mean	*% or Standard deviation*	
Sex	Female	n = 175	*40.9%*	n = 167	*41.9%*	n = 8	*27.6%*	
	Male	n = 253	*59.1%*	n = 232	*58.1%*	n = 21	*72.4%*	0.1313
Race	White	n = 181	*42.3%*	n = 173	*43.4%*	n = 8	*27.6%*	0.1727
	Black/African American	n = 191	*44.6%*	n = 176	*44.1%*	n = 15	*51.7%*	
	American Indian/Alaskan, Hawaiian Native/Other Pacific Islander	n = 8	*1.9%*	n = 6	*1.5%*	n = 2	*6.9%*	
	Asian	n = 14	*3.3%*	n = 13	*3.3%*	n = 1	*3.4%*	
	Other	n = 34	*7.9%*	n = 31	*7.8%*	n = 3	*10.3%*	
Ethnicity	Hispanic or Latino	N = 34	*7.9%*	N = 31	*7.8%*	N = 3	*10.3%*	0.4946
	Non-Hispanic or Latino	n = 394	*92.1%*	n = 368	*92.2%*	n = 26	*89.7%*	
Comorbidities	Vascular Disease	n = 19	*4.4%*	n = 18	*4.5%*	n = 1	*3.4%*	1.0
	Diabetes Mellitus	n = 81	*18.9%*	n = 74	*18.5%*	n = 7	*24.1%*	0.4629
	Age at transplant	49.8	*13.2*	49.3	*13.3*	56.5	*10.5*	0.0053
	Body Mass Index	28.4	*5.4*	28.3	*5.4*	28.6	*6*	0.7867
	Creatinine Highest	8.7	*4*	8.7	*4*	9.6	*3.8*	0.1624
	Creatinine before Discharge	1.9	*1.8*	1.9	*1.8*	2.1	*1.3*	0.2261
	CHA2DS2_VASc	2.1	*0.9*	2.1	*0.9*	2.1	*1.1*	0.9280
	HAS_BLED			3.6	*1.1*	4	*1.1*	0.0604
Outcomes	Bleeding	n = 216	*50.5%*	n = 198	*49.6%*	n = 18	*62.1%*	0.1956

	Any Intervention	n = 30	*7%*	n = 24	*6%*	n = 6	*20.7%*	**0.0219**
	Surgical Intervention	n = 20	*4.7%*	n = 16	*4%*	n = 4	*13.8%*	**0.0386**
	Dialysis	n = 93	*21.7%*	n = 81	*20.3%*	n = 12	*41.4%*	**0.0169**
	Mean Length of Stay	6.7	*8.4*	6.2	*4*	14.6	*27.7*	**0.0114**
	Readmission after Discharge	n = 89	*20.8%*	n = 79	*19.8%*	n = 10	*34.5%*	0.0929
	Follow up period	6 months						
	Overall	n = 43	*10%*	n = 28	*7%*	n = 15	*51.7%*	**<0.0001**
	Warfarin	n = 20	*4.7%*	n = 9	*2.3%*	n = 11	*37.9%*	**<0.0001**
	Enoxaparin	n = 9	*2.1%*	n = 7	*1.8%*	n = 2	*6.9%*	0.1187
Anticoagulation	Apixaban	n = 5	*1.2%*	n = 3	*0.8%*	n = 2	*6.9%*	**0.0391**
	Heparin	n = 23	*5.4%*	n = 16	*4%*	n = 7	*24.1%*	**0.0004**
	Clopidogrel	n = 6	*1.4%*	n = 6	*1.5%*	n = 0	*0%*	1.0
	Fondaparinux	n = 1	*0.2%*	n = 1	*0.3%*	n = 0	*0%*	1.0

4.1 Blood Thinners Versus Interventions

In our cohort, 6.8% of patients (n = 29/428) had AF and 51.7% (n = 15/29) of the AF patients received AC in the early post-operative period. Of those, 73.3% (n = 11/15) had a post-operative bleed. Of these patients who were diagnosed with a bleed post-operatively, 36.4% (n = 4/11) required an intervention (surgical or percutaneous intervention). In comparison, 93.2% (n = 399/428) of the patients in our cohort did not have AF. Of these patients, 7% (n = 28/399) received anticoagulation therapy due to a history of venous thrombus, mechanical valve, or similar indications. Out of these patients, 60.7% (n = 17/28) were diagnosed with a bleeding complication. Of those who had a post-operative bleed on AC, 29.4% (n = 5/17) required an intervention. When evaluating all kidney transplant recipients, regardless of AC administration, 50.5% (n = 216/428) were diagnosed with a decrease in their hemoglobin by at least 2 g/dl (Table 1). Of all the patients who were diagnosed with a bleed, 13.4% (n = 29/216) of patients required intervention. Additionally, no patient experienced stroke or TIA during our study.

AC use positively correlates with multiple variables examined in this study. Of note, post-transplant use of AC was associated with increased odds of having an intervention for subsequent bleeding events. Specifically, these patients had nearly five times higher odds of requiring an intervention post-transplant (Odds Ratio [OR] = 4.62, 95% Confidence Interval [CI]: 1.63-13.13, p = 0.0041). Additionally, they also had seven times higher odds of post-transplant surgery/return to the operating room (OR = 7.34, 95% CI: 2.32-23.25, p = 0.0007), to stop the hemorrhage (Table 2).

Table 2 Summary statistics of study outcomes by atrial fibrillation status.

Characteristic	Categories	Overall, n = 428		No atrial fibrillation		Atrial fibrillation			Dialysis 1week: No atrial fibrillation		Dialysis 1week: Atrial fibrillation		
		Frequency or Mean	*% or Standard deviation*	Frequency or Mean	*% or Standard deviation*	Frequency or Mean	*% or Standard deviation*	p-value	Frequency or Mean	*% or Standard deviation*	Frequency or Mean	*% or Standard deviation*	p-value
Total sample size		N = 428	*100%*	399	*93.2%*	29	*6.8%*		81	*20.3%*	12	*41.4%*	
Anticoagulation													
	No	N = 385	*90%*	371	*93%*	14	*48.3%*	<0.0001	69	*85.2%*	5	*41.7%*	*0.0022*
	Yes	N = 43	*10%*	28	*7%*	15	*51.7%*	0.5118	12	*14.8%*	7	*58.3%*	
Bleed													
	No anticoagulation	N = 188	*48.8%*	181	*48.8%*	7	*50%*	1.0000	46	*66.7%*	5	*100%*	*0.0309*
	Anticoagulation	N = 28	*65%*	17	*60.7%*	11	*73.3%*	0.2488	9 (75%)	*75%*	5	*71.4%*	
Intervention													
	No anticoagulation	N = 20	*10.6%*	18	*4.9%*	2	*14.3%*	0.1737	3	*4.35%*	1	*20%*	*1.0000*
	Anticoagulation	N = 9	*32.1%*	5	*17.9%*	4	*26.7%*	0.6960	1	*8.33%*	1	*14.3%*	

Clinically, an increase in HAS-BLED scores is associated with poorer post-transplant outcomes. For instance, a unit increase in HAS-BLED is associated with 61% higher odds of having an intervention and is statistically significant (OR = 1.61, 95% CI: 1.1-2.36, p = 0.0143) (Table 3).

Table 3 Odds Ratio Estimates for intervention, surgical intervention, dialysis within one-week post-transplant, and readmission.

	Odds Ratio Estimates for the predictors of having any intervention			**Odds Ratio Estimates for the predictors of having a surgery**			**Odds Ratio Estimates for the predictors of dialysis within one-week post-transplant**			**Odds Ratio Estimates for the predictors of readmission**		
Characteristic (predictor)	**Odds Ratio**	**Confidence Interval (95%)**	**p-value**	**Odds Ratio**	**Confidence Interval (95%)**	**p-value**	**Odds Ratio**	**Confidence Interval (95%)**	**p-value**	**Odds Ratio**	**Confidence Interval (95%)**	**p-value**
Atrial fibrillation: Yes vs No	1.95	(0.57, 6.64)	0.2836	1.76	(0.42, 7.37)	0.439	1.52	(0.57, 4.06)	0.4041	0.86	(0.32, 2.33)	0.7707
Sex: Female vs Male	1.12	(0.49, 2.53)	0.7896	0.88	(0.32, 2.44)	0.8119	0.54	(0.31, 0.92)	**0.0234**	0.63	(0.38, 1.07)	0.0892
Age	1.00	(0.97, 1.04)	0.877	1.00	(0.97, 1.04)	0.8634	1.01	(0.99, 1.03)	0.5223	1	(0.98, 1.02)	0.8084
Race: American Indian/Alaskan, Hawaiian Native/Other Pacific Islander vs White	<0.001	(<0.001, >999.999)	0.9642	<0.001	(<0.001, >999.999)	0.9666	0.64	(0.06, 7.07)	0.5196	3.01	(0.62, 14.71)	0.1601
Asian vs White	2.78	(0.51, 15.31)	0.9456	4.56	(0.77, 27.06)	0.9435	0.74	(0.09, 6.13)	0.5761	0.32	(0.04, 2.73)	0.1556
Black/African American vs White	0.76	(0.31, 1.89)	0.967	0.70	(0.23, 2.17)	0.9728	2.38	(1.35, 4.18)	0.1018	1.16	(0.67, 2.01)	0.9616
Other: Race vs White	0.31	(0.03, 3.56)	0.982	0.37	(0.02, 5.68)	0.9829	2.48	(0.34, 18.30)	0.4158	1.75	(0.32, 9.69)	0.5658
Hispanic: Yes vs No	4.86	(0.51, 45.97)	0.1681	5.69	(0.48, 66.96)	0.1666	0.51	(0.06, 4.23)	0.5358	0.47	(0.08, 2.90)	0.4185
Any Anticoagulant: Yes vs No	4.62	(1.63, 13.13)	**0.0041**	7.34	(2.32, 23.25)	**0.0007**	3.27	(1.45, 7.35)	**0.0042**	3.9	(1.80, 8.48)	**0.0006**
Vascular Disease: Yes vs No	0.61	(0.06, 5.74)	0.6643	1.74	(0.17, 18.31)	0.646	0.93	(0.27, 3.17)	0.9102	0.57	(0.17, 1.96)	0.3732
Diabetes Mellitus: Yes vs No	3.02	(1.01, 9.05)	**0.0482**	2.54	(0.67, 9.55)	0.1691	2.26	(1.09, 4.69)	**0.0278**	1.56	(0.76, 3.21)	0.2298
Body Mass Index (BMI)	0.96	(0.88, 1.05)	0.3506	0.98	(0.89, 1.08)	0.6788	1.07	(1.02, 1.13)	**0.0035**	0.99	(0.95, 1.04)	0.8048
CHA2DS2_VASc	0.53	(0.31, 0.92)	**0.0252**	0.65	(0.32, 1.32)	0.2278	1.00	(0.70, 1.43)	0.9952	1.04	(0.74, 1.47)	0.8127
HAS_BLED	1.61	(1.10, 2.36)	**0.0143**	0.88	(0.52, 1.50)	0.6418	0.93	(0.71, 1.23)	0.6139	1.37	(1.06, 1.78)	**0.0168**
Any Intervention: Yes vs No	-	-	-	-	-	-	0.34	(0.04, 3.27)	0.3487	0.22	(0.02, 1.97)	0.1737
Surgery: Yes vs No	-	-	-	-	-	-	2.52	(0.20, 31.97)	0.4753	7.87	(0.70, 88.01)	0.0941

When evaluating the use of AC in relation to creatinine values, patients on AC had significantly higher serum creatinine at discharge compared to those who were not on AC. Specifically, patients who received AC exhibited a 1.2 increase in serum creatinine compared to their last creatinine at discharge (Estimate 1.22, 95% CI: 0.62-1.83, p < 0.0001) (Table 4).

Table 4 Estimates for predictors of creatinine values both highest in value and final value before discharge.

	Estimates for predictors of highest creatinine value			**Estimates for predictors of Creatinine (last value before discharge)**		
Characteristic (predictor)	**Estimate**	**Confidence Interval (95%)**	**p-value**	**Estimate**	**Confidence Interval (95%)**	**p-value**
Atrial Fibrillation: Yes vs No	0.21	(-1.20, 1.62)	0.7695	-0.61	(-1.33, 0.12)	0.1016
Sex: Female vs Male	-2.00	(-2.66, -1.34)	**<0.0001**	-0.71	(-1.05, -0.37)	**<0.0001**
Age	-0.07	(-0.09, -0.04)	**<0.0001**	0.01	(-0.01, 0.02)	0.3971
Race: American Indian/Alaskan, Hawaiian Native/Other Pacific Islander vs White	4.71	(2.29, 7.12)	**0.0002**	-0.14	(-1.39, 1.10)	0.8235
Asian vs White	2.21	(0.35, 4.07)	**0.0203**	0.02	(-0.94, 0.98)	0.9697
Black/African American vs White	3.75	(3.04, 4.46)	**<0.0001**	0.58	(0.22, 0.95)	**0.0017**
Other: Race vs White	0.15	(-2.05, 2.36)	0.8903	0.10	(-1.03, 1.23)	0.8614
Hispanic: Yes vs No	1.24	(-0.98, 3.45)	0.2723	-0.01	(-1.15, 1.13)	0.987
Any Anticoagulant: Yes vs No	0.58	(-0.59, 1.76)	0.3312	1.22	(0.62, 1.83)	**<0.0001**
Vascular Disease: Yes vs No	-0.51	(-2.18, 1.16)	0.5478	0.12	(-0.74, 0.98)	0.7764
Diabetes Mellitus: Yes vs No	-0.97	(-1.99, 0.05)	0.0626	-0.19	(-0.72, 0.34)	0.4778
Body Mass Index (BMI)	0.05	(-0.01, 0.11)	0.1009	0.05	(0.02, 0.08)	**0.0038**
CHA2DS2_VASc	0.07	(-0.40, 0.54)	0.7679	0.08	(-0.16, 0.33)	0.5064
HAS_BLED	0.23	(-0.13, 0.59)	0.2097	-0.07	(-0.25, 0.12)	0.4776
Any Intervention: Yes vs No	-0.22	(-2.41, 1.98)	0.847	0.80	(-0.33, 1.93)	0.1672
Surgery: Yes vs No	0.49	(-2.15, 3.13)	0.7153	-0.16	(-1.52, 1.20)	0.8211

Additionally, AC use was associated with an increased odds of the patient having delayed graft function. Patients who received AC had three times higher odds of dialysis post-transplant (OR = 3.27, 95% CI: 1.45-7.35, *p* = 0.0042) (Table 3).

In our evaluation of LOS for individuals in our cohort, patients receiving AC had 1.61 times longer LOS than those who did not (RR = 1.61, 95% CI: 1.17-2.23, *p* = 0.0038748) and patients using AC also had a four times higher odds of readmission (OR = 3.98, 95% CI: 1.80-8.48, *p* = 0.0006) (Table 5). As mentioned above, patients had a higher likelihood of requiring post-surgical intervention if they had an increased HAS-BLED score. This is important when investigating readmission rates, as a 1-unit increase in HAS-BLED score was also shown to be associated with 37% higher odds of readmission (OR = 1.37, 95% CI: 1.06-1.78, *p* = 0.0168) (Table 3).

Table 5 Relative Risk for predictors of length of stay for patients.

Characteristic (predictor)	Relative Risk	Confidence Interval (95%)	p-value
Atrial Fibrillation: Yes vs No	1.47	(0.97, 2.25)	0.07183
Sex: Female vs Male	0.97	(0.86, 1.10)	0.6860
Age	1.01	(1.00, 1.01)	0.06082
Race: American Indian/Alaskan, Hawaiian Native/Other Pacific Islander vs White	0.92	(0.67, 1.26)	0.5985
Asian vs White	0.99	(0.76, 1.29)	0.9535
Black/African American vs White	1.17	(1.00, 1.37)	**0.04318**
Other: Race vs White	1.13	(0.89, 1.42)	0.3204
Hispanic: Yes vs No	0.77	(0.60, 0.98)	**0.03359**
Any Anticoagulant: Yes vs No	1.61	(1.17, 2.23)	**0.003875**
Vascular Disease: Yes vs No	1.13	(0.82, 1.56)	0.4547
Diabetes Mellitus: Yes vs No	1.52	(1.10, 2.11)	**0.01115**
Body Mass Index (BMI)	1.00	(0.99, 1.01)	0.9520
CHA2DS2_VASc	0.94	(0.84, 1.06)	0.3187
HAS_BLED	0.92	(0.84, 1.02)	0.09829
Any Intervention: Yes vs No	1.32	(0.67, 2.60)	0.4152
Surgery: Yes vs No	1.93	(0.87, 4.31)	0.1081

5. Discussion

To the best of our knowledge, this is the first study that evaluates the risk of AC and early post-operative bleeding in kidney transplant recipients with AF. Our primary goal is to bridge the existing gap in guidelines concerning AF management in kidney transplant recipients, a population often facing unique challenges. Widely utilized risk assessment tools, such as CHA_2DS_2-VASc and HAS-BLED scores, are primarily designed for non-surgical scenarios and offer projections for stroke and bleeding risks over a one-year period, without factoring in the minimal daily stroke risk and elevated daily morbidity rate associated with initiating AC therapy. As a result, these tools may not adequately consider the specific risks associated with surgical interventions, potentially underestimating the risk of bleeding in kidney transplant recipients or patients immediately post-operative.

The findings presented in this study offer valuable insights into the impact of AC use on post-transplant outcomes. It underscores the negative impact AC can have on post-kidney transplant patients, emphasizing the need for cautious administration in patients who recently underwent surgery. Notably, patients receiving AC exhibited a fivefold increase in the likelihood of requiring post-transplant interventions, and a sevenfold increase in the likelihood of returning to the operating room. These findings emphasize the necessity for re-evaluating AC management strategies post-kidney transplant and highlight the potential need for a novel scoring system tailored for this population in the future. Furthermore, our investigation revealed threefold higher odds of

dialysis within one-week post-transplant among patients receiving AC, highlighting the intricate interplay between AC use, bleeding risk, and kidney function.

Increased rates of readmission and post-transplant dialysis pose significant challenges to both patients and the healthcare system. Returning to dialysis or undergoing post-transplant intervention due to bleeding is resource-intensive and directly opposes the primary objective of transplantation. Additionally, bleeding complications (e.g., formation of large hematomas), can be a nidus for infection, exert pressure on the kidney graft, or lead to further hemorrhage [21, 22]. These complications often necessitate medical interventions and may prolong hospital stays [21]. Likewise, managing bleeding-related side effects and complications typically requires increased use of medications, outpatient services, and monitoring, all of which contribute to higher overall healthcare costs [21, 23]. Thus, maintaining hemodynamic stability is crucial not only for enhancing the patient's quality of life but also for mitigating the economic impact on the healthcare system [24].

Furthermore, the association between AC usage and adverse post-transplant outcomes extends beyond bleeding complications. The findings of this study highlight significant associations between the use of AC and various clinical outcomes, particularly LOS and readmission rates, in our cohort. The observed 1.61 times longer LOS in patients receiving AC compared to those who did not suggest that AC usage is a substantial factor in prolonged hospitalization. This increased LOS could be attributed to the need for meticulous monitoring of anticoagulation therapy, management of potential bleeding complications, or other AC-related adverse events.

In addition, the fourfold increase in the odds of readmission for patients on AC underscores the critical impact of anticoagulation on patient outcomes beyond the initial hospital stay. This elevated readmission risk could stem from several factors, including complications from bleeding, the need for continued medical oversight, or issues related to AC management post-discharge. These findings suggest that while AC therapy is essential for preventing thromboembolic events in certain patient populations, it also poses significant challenges in the postoperative period.

The association between an increased HAS-BLED score and higher odds of readmission further complicates the landscape of patient management. The HAS-BLED score, used to assess the risk of bleeding in patients on anticoagulation therapy, seems to be a valuable predictive tool for readmission risk. A 1-unit increase in HAS-BLED score correlates with a 37% higher likelihood of readmission. A previous study demonstrates HAS-BLED scores have good accuracy in predicting bleeding events and allograft failure in kidney transplant recipients [23]. Notably, they found starting anticoagulation within 6 hours after kidney transplant significantly predicts postoperative bleeding [22]. Additionally, there was a close relationship between postoperative bleeding episodes and elevated HAS-BLED scores in kidney transplant patients, which led to worse long-term outcomes, such as higher rates of graft failure and patient death [22]. These findings highlight the importance of avoiding premature initiation of anticoagulant medications during the crucial early postoperative period following kidney transplantation.

Moreover, our investigation revealed a concerning trend: patients on AC had significantly higher creatinine levels at discharge compared to admission, suggesting compromised renal function [25]. This highlights the importance of closely monitoring renal function in post-transplant patients receiving AC, as bleeding related to AC use can exacerbate kidney dysfunction, potentially leading to longer hospital stays and compromised graft survival.

Despite being a more expensive medication in the short-term, when compared to warfarin, direct oral anticoagulants (DOACs) are preferable due to their associated shorter hospitalization periods and decreased healthcare costs, attributable to their reduced monitoring needs compared to warfarin [26]. DOACS offer several potential advantages in terms of bleeding risk, earlier discharge, and decreased monitoring, but have not been studied extensively in post-transplant patients. Given the difficulty of reversing these agents, many transplant centers are reticent to initiate these agents in the early post-operative window when interventions such as graft biopsy, wound re-explorations, or drain placements are still prevalent. For these reasons, our study utilized warfarin and heparin. Should DOACS become more commonly utilized in this early post-operative window, our study can be a reasonable benchmark in assessing their efficacy. Also, our research was constrained by the small cohort of patients receiving anticoagulation, limiting our capacity to thoroughly compare the outcomes across different AC classes. The sample size and small number of events may also affect the precision and wide confidence intervals associated with some estimates. In addition, our data is from a single center, which may limit the generalizability of the findings. Future studies should consider using data from more centers to increase precision and generalizability of results.

Our study included all kidney transplant recipients who received AC as a proxy for those with AF who received AC. This allowed us to gather broader insights into the impact of AC on post-transplant outcomes, such as bleeding risk, length of stay, and readmission rates. The physiological effects of AC are relevant across different indications, making this approach useful for understanding the general challenges of AC in kidney transplant recipients. It also provided a more robust dataset, leading to more meaningful conclusions about AC's risks and benefits in this population.

Furthermore, since the demographics and risk factors between AF patients and the rest of the kidney transplant recipients did not significantly differ, the internal validity of the study is strengthened. The key difference noted was in age, as shown in Table 1: AF patients had a mean age of 56.5 ± 10.5 years, while those without AF were younger, with a mean age of 49.3 ± 13.3 years. However, risk factors such as highest creatinine, creatinine before discharge, BMI, CHA_2DS_2-VASc, and HAS-BLED did not differ significantly between the groups. The similarity in baseline characteristics means the findings from the broader AC-receiving population can be more reliably generalized to those specifically with AF, making the study's results more applicable to the AF cohort while maintaining its overall validity. However, it's important to note that using a broader population still introduces some heterogeneity in clinical indications for AC, which could slightly influence the outcomes and is a limitation to this study. This highlights the need for larger, more targeted studies focused specifically on kidney transplant recipients with AF to better assess the unique risks and benefits of AC in this group.

Our findings underscore the intricate balance clinicians must maintain when initiating AC therapy in kidney transplant recipients with AF, considering its implications not only for bleeding risk but also for graft function, length of stay, and readmission rates. When comparing the observed association between higher CHA_2DS_2-VASc and HAS-BLED scores and poorer post-transplant outcomes, we highlight the importance of a pre/post-transplant risk assessment tool. Our study emphasizes the importance of linking these scores with post-transplant complications, thereby facilitating the development of risk stratification tools in transplant medicine.

6. Conclusion

Our study highlights the complexities of managing anticoagulation in fresh kidney transplant recipients with atrial fibrillation. While anticoagulants are pivotal in stroke prevention, their use in the post-transplant period is linked with bleeding and increased risk for additional interventions, higher odds of returning to surgery, and elevated risks of delayed graft function. The impact also extends to length of stay and readmission rates. These findings raise important questions about the current management of anticoagulation therapy in this patient population. Furthermore, our study highlights the inadequacies of current risk assessment tools like CHA_2DS_2-VASc and HAS-BLED in accounting for bleeding risks post-transplant. There is a clear need for a specific stratification tool that considers post-transplant dynamics and anticipates the heightened risks associated with anticoagulation in this setting. In summary, anticoagulation early post-transplant carries significant risk not appreciated in currently used algorithms. Management of these patients requires a balanced and personalized approach with vigilant postoperative monitoring to optimize patient outcomes and reduce healthcare costs.

Author Contributions

Maria V. Fonseca Bauza: performed data collection, conducted literature review, wrote the initial draft, prepared figures and tables, participated in manuscript editing, and coordinated revisions among authors. Aimee H. Dubin: performed data collection, conducted literature review, wrote the initial draft, prepared figures and tables, participated in manuscript editing, and coordinated revisions among authors. Chris B. Agala: Performed statistical analysis and contributed to manuscript drafting. Alexander H. Toledo: Provided technical expertise, reviewed the methodology, and assisted in data interpretation. Kristen R. Szempruch: Provided technical expertise and assisted in data interpretation. David A. Gerber: Provided technical expertise and contributed to discussion and conclusions. Pablo Serrano Rodriguez: Conceived and designed the study, supervised the project, and provided critical revisions to the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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