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Effect of Direct Oral Anticoagulants Versus Warfarin on Patency in High-Risk Bypass Patients

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Background: The use of warfarin for anticoagulation in thromboembolic disease has been the mainstay of treatment. Direct oral anticoagulants (DOACs) have demonstrated equivalent anticoagulant effects, without increased bleeding risks or need for frequent monitoring. However, the role of DOACs remains unclear in the setting of replacing warfarin for high-risk peripheral artery disease (PAD) interventions. The purpose of this study is to evaluate the efficacy of DOACs compared to warfarin during the postoperative period in patients that underwent a lower extremity high-risk bypass (HRB).

Methods: The study is a single institution, retrospective review of all lower extremity HRBs between January 2012 and June 2021, who were previously placed on or started on anticoagulation with a DOAC or warfarin. The HRB group included all patients undergoing femoral to above or below knee bypass with an adjunct procedure, or below knee bypass with synthetic or composite vein conduit. All demographics, preoperative factors, and complications were evaluated with respect to DOAC versus warfarin.

Results: A total of 44 patients (28 males; average age 68.8 ± 10.9) underwent an HRB during the study period. There were no significant differences in demographics and preoperative characteristics between the 2 groups. Among patient comorbidities, coronary artery disease was found to be significantly higher in patients on DOACs ($P = 0.03$). The 12-month primary patency rate was 83.3% versus 57.1%, for DOAC versus warfarin respectively ($P = 0.03$). Multivariate analyses revealed that <30-day reinterventions contribute to 12-month patency ($P = 0.02$).

Conclusions: Patients who underwent lower extremity HRB with postoperative DOAC appeared to exhibit higher graft patency rates than those who were placed on warfarin. Due to their low incidence of undesirable side effects and the lack of frequent monitoring, DOACs could be considered a safe alternative to warfarin in the postoperative period for patients with HRB.

INTRODUCTION

Maintaining long-term patency of high-risk infrainguinal lower extremity bypass grafts is challenging. Factors which increase the risk for graft failure are well known.[1] High-risk bypass (HRB) grafts are defined as those which are performed due to unfavorable or unavailable autogenous veins requiring the need for prosthetic or hybrid graft insertion. Redo bypass surgery has also been classified as ''high risk''.[2,3] Antithrombotic therapy has been the mainstay of treatment for postoperative HRB management. Several studies comparing the efficacy of antiplatelet to warfarin therapy in the

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postoperative period have found anticoagulation with warfarin to be associated with a higher rate of graft patency.[4–7] One study from the Vascular Quality Initiative registry found no significant difference in anticoagulation usage in the 1-year patency of lower extremity bypass patients, but suggested increased patency in a subset of patients who received a prosthetic bypass graft.[8] However, placing a patient on warfarin requires an initial titration period and regular outpatient international normalized ratio (INR) level monitoring due to its narrow therapeutic window and increased risk of bleeding complications. Therapeutic INR levels can vary from 2.0 to 4.0 depending on institution and ensuring patient compliance for regular blood draws can be challenging for providers.[9,10]

Direct oral anticoagulants (DOACs), like dabigatran, apixaban, rivaroxaban, and edoxaban, have been shown to have equivalent anticoagulant effects with a decreased incidence of bleeding complications in patients with atrial fibrillation and venous thromboembolism, without the need for frequent monitoring. However, the role of DOACs remains unclear in the setting as an alternative to warfarin for high-risk peripheral artery disease (PAD) interventions. A recent retrospective study found similar postoperative patency and complication outcomes in peripheral bypass patients receiving a DOAC or vitamin K antagonist, although patients on DOACs had a shorter hospital stay and were less likely to receive a blood transfusion.[11] That same study found a majority of surgeons have adopted the use of DOACs in bypass procedures, despite lack of established evidence on their safety and efficacy in patients requiring anticoagulation in high-risk bypass patients.

The purpose of this study is to compare the patency of lower extremity HRB between patients on DOACs and on warfarin in the postoperative period. We hypothesize that patients undergoing HRB and treated with DOACs will maintain equivalent patency to those treated with warfarin.

METHODS

This is an Institutional Review Board-approved (study #2021−04-03-MMC IRB) retrospective pilot study of all lower extremity HRB patients at a single center between January 2012 and June 2021, who were previously placed on or started on an anticoagulant medication. The HRB group included all patients undergoing infrainguinal composite, sequential, or interposition bypasses. Composite bypasses included those with either spliced vein or spliced polytetrafluoroethylene. Patients were also included if their procedure was a redo bypass or required an intraoperative adjunct procedure to improve inflow and/or outflow. Adjunct procedures included vein cuffs, endarterectomies, thrombolysis/thrombectomies, and/or endovascular interventions. Distal bypass targets ranged from above knee popliteal to tibial arteries. We categorized these patients into 2 groups: those continued or started on warfarin ($N = 18$), and those continued or started on a DOAC ($N = 26$). DOAC patients were on either apixaban or rivaroxaban. The decision to place a patient on either warfarin or a DOAC was left to surgeon preference at the time of the procedure. More patients were prescribed warfarin in the earlier years of the study with a shift towards DOACs in the last few years. Patients with identified financial issues were addressed accordingly during their stay. Patients only on antiplatelet therapy were excluded from the study.

Preoperative demographics and comorbidities were obtained from all patients from their medical records. Demographics included age, sex, and race. Comorbidities included a prior history of diabetes mellitus, hypertension, hyperlipidemia, stroke, myocardial infarction, venous thromboembolism/pulmonary embolism, coronary artery disease, peripheral arterial disease, chronic kidney disease, end-stage renal disease on hemodialysis, congestive heart failure, chronic obstructive pulmonary disease, and/or atrial fibrillation. Preoperative patient characteristics were also collected, including a prior history of angioplasty or stent, and whether their symptoms at the time of surgery were claudication or critical limb-threatening ischemia. All femoropopliteal lesions were classified according to the TransAtlantic Inter-Society Consensus (TASC) and the number of run-off vessels were documented.

Primary outcome was 12-month primary bypass patency, defined as <50% stenosis seen in lower extremity arterial graft duplexes during outpatient follow-up appointments, in line with Society for Vascular Surgery reporting guidelines for lower extremity ischemia.[12] Secondary outcomes included less than 30-day reinterventions, greater than 30-day reinterventions, bleeding complications (e.g., need for transfusion, hematoma, gastrointestinal bleeding, hematuria), cerebrovascular or cardiovascular complications (e.g., stroke, myocardial infarction), subsequent need for major amputation, and mortality.

All demographics, preoperative factors, and complications were summarized using the Fisher's Exact test. For age, medians and 25th−75th percentiles were used, and compared across groups using the

Mann-Whitney *U* statistic. A Kaplan-Meier curve comparing patency survival probability over the 12-month period between the 2 groups was also produced. A log-rank result was calculated to determine the statistical significance between patency among the 2 groups. A series of multivariate binary logistic regression analyses were run to test the effect of individual covariates on the predictive ability of anticoagulation group on patency. Each model was compared to the base model of group effect on outcome by model fit (AIC, SC, and -2LogL) and r-square power (Cox-Snell). All analyses were conducted using SAS v9.4 and significance was set as $P < 0.05$.

RESULTS

A total of 44 patients (28 males; average age 69.4 ± 10.6 years for DOAC vs. 67.9 ± 11.5 years for warfarin) underwent an HRB during the study period. Overall, there was no statistically significant difference in demographics and pre-operative characteristics between the 2 groups (Table I). Sixty-five percent of the patients in the DOAC group and 61% of the patients in the warfarin group were male ($P = 1.00$). Caucasians made up 65% of the patients in the DOAC group patients, as compared to 56% of the same in the warfarin group; while 31% of the patients in the DOAC group were African-American, compared to 22% of the patients in the warfarin group ($P = 0.06$).

Among patient comorbidities, 65% of the patients on a DOAC had a history of coronary artery disease; in comparison, only 28% of the patients on warfarin had this history ($P = 0.03$). Otherwise, there was no difference in the frequency of other comorbidities between the 2 groups. Most patients had a history of smoking, diabetes mellitus, hypertension, and peripheral arterial disease. Sixty-two percent of the DOAC patients and 56% of the warfarin patients had a previous angioplasty before their HRB procedure ($P = 0.76$); 50% in each group had previous endovascular intervention with stent placement ($P = 1.00$) while 23% of the patients on DOAC and 39% of the patients on warfarin had a previous bypass ($P = 0.32$). Ninety-two percent of the DOAC group and 83% of the warfarin group had a diagnosis of critical limb-threatening ischemia prior to surgery ($P = 0.32$). All the patients in the DOAC group and 81% of the patients in the warfarin group were classified as TASC C or D ($P = 0.10$). Fifty percent of the patients in the DOAC group had either 0- or 1-vessel tibial runoffs, compared to 62.6% of the patients in the warfarin group ($P = 0.38$). Seventeen percent of the patients in the DOAC group had 3-vessel runoff, compared to 0% in the warfarin group ($P = 0.38$). Post-hoc results did not find any difference in tibial runoff frequencies between the 2 groups.

There was a statistically significant difference in the 12-month patency rate of HRB in patients placed on a DOAC as compared to those on warfarin when looking at the Kaplan-Meier survival curve. The primary patency rate at the 12-month follow-up in the DOAC group was 83.3%, compared to 57.1% in the warfarin group (Fig. 1). Log-rank results supported that the observed differences in graft patency between DOAC and warfarin were significant ($P = 0.03$). There was no difference in postoperative outcomes and complications between DOAC and warfarin patients (Table II). Multivariate analyses showed that >30-days postoperative reinterventions contributed significantly to 12-month patency ($P < 0.001$). Odds ratio scores indicate that when controlling for >30-day reinterventions, HRBs in DOAC patients had 6.6 times greater odds of being patent at 12 months than in those on warfarin (OR = 6.59, CI 1.06−41.09); without reinterventions the bypasses were 23 times more likely to be patent (odds ratio OR = 23.16, confidence interval CI 3.72−144.06). All other demographic, preoperative factors, and complications did not significantly contribute to the prediction of patency ($P > 0.05$).

DISCUSSION

Since the U.S. Food and Drug Administration approval of several types of DOACs, this class of anticoagulants has emerged as an attractive adjunctive option in cardiovascular and vascular treatment.[13] Although first utilized as treatment for atrial fibrillation and venous thromboembolism as a noninferior or superior alternative to vitamin K antagonists, their indications have expanded recently to other disease processes like CAD and PAD.[14] Among DOACs, rivaroxaban specifically has been studied through 2 separate randomized double-blind trials. The COMPASS trial included over 27,000 patients with stable CAD and/or PAD and randomized them to 3 treatment arms: rivaroxaban-plus-aspirin, rivaroxaban, or aspirin. The study was stopped due to superiority in the rivaroxaban-plus-aspirin group.[15] Similarly, the VOYAGER PAD trial randomized over 6,500 patients with PAD undergoing lower-extremity revascularization procedures to treatment with either rivaroxaban-plus-aspirin or placebo-plus-aspirin and found rivaroxaban to be superior to placebo in post-operative complications.[16]

Table I. Patient demographics, pre-operative characteristics, and operations

	DOAC ($N = 26$)	Warfarin ($N = 18$)	
	Mean (SD)/%	Mean (SD)/%	*P*
Demographics			
Age	69.4 (10.6)	67.9 (11.5)	0.661
Gender			1.000
Male	65.4%	61.1%	
Female	34.6%	38.9%	
Race/Ethnicity			0.055
White	65.4%	55.6%	
Black	30.8%	22.2%	
Asian	3.9%	0.0%	
Hispanic	0.0%	22.2%	
Comorbidities			
Diabetes Mellitus	57.7%	61.1%	1.000
Insulin Dependent	38.5%	22.2%	
Non-Insulin Dependent	15.4%	38.9%	
Hypertension	84.6%	83.3%	1.000
Hyperlipidemia	53.9%	33.3%	0.227
Stroke	30.8%	5.6%	0.060
Myocardial Infarction	26.9%	11.1%	0.270
VTE/PE	19.2%	11.1%	0.682
Coronary Artery Disease	65.4%	27.8%	**0.031**
Peripheral Arterial Disease	92.3%	83.3%	0.386
Chronic Kidney Disease	15.4%	11.1%	1.000
End-Stage Renal Disease on Hemodialysis	15.4%	5.6%	0.634
Congestive Heart Failure	23.1%	11.1%	0.439
Chronic Obstructive Pulmonary Disease	34.6%	16.7%	0.304
Atrial Fibrillation	19.2%	5.6%	0.375
Smoking	76.9%	77.8%	1.000
Former Smoker	46.1%	27.8%	
Current Smoker	30.8%	50.0%	
Pack-Years	38.2 (27.83)	32.4 (15.6)	
Pre-Operative Characteristics			
Previous Angioplasty	61.5%	55.6%	0.761
Previous Stent	50.0%	50.0%	1.000
Critical Limb Threatening Ischemia	92.3%	83.3%	0.386
TASC Classification			0.100
A	0.0%	6.3%	
B	0.0%	12.5%	
C	62.5%	37.5%	
D	37.5%	43.8%	
Tibial Vessel Run-Off			0.383
0	8.3%	18.8%	
1	41.7%	43.8%	
2	33.3%	37.5%	
3	16.7%	0.0%	
Operations			
Bypass Targets			
Above Knee Popliteal			
PTFE	46.2%	5.6%	**0.043**
Vein	3.85%	0.0%	0.676
Below Knee Popliteal			
PTFE	7.7%	16.7%	0.386
Vein	11.5%	22.2%	0.419

(*Continued*)

Table I. Continued

	DOAC ($N = 26$)	Warfarin ($N = 18$)	
	Mean (SD)/%	Mean (SD)/%	*P*
Tibioperoneal Trunk or Tibial			
PTFE	7.7%	22.2%	0.208
Vein	23.1%	33.3%	0.506
High-Risk Criteria			
Redo Bypass	26.9%	38.9%	0.515
Composite/Sequential/Interposition Bypass	30.8%	33.3%	1.000
Adjunct Procedure[a]			
Endarterectomy	80.8%	27.8%	**0.001**
Thrombolysis/Thrombectomy	15.4%	50.0%	**0.020**
Endovascular	42.3%	11.1%	**0.043**
Vein Cuff	11.5%	16.7%	0.676

PTFE, polytetrafluoroethylene.
Bold indicates $P < 0.05$.
[a]Some patients had more than 1 adjunct procedure during the index operation.

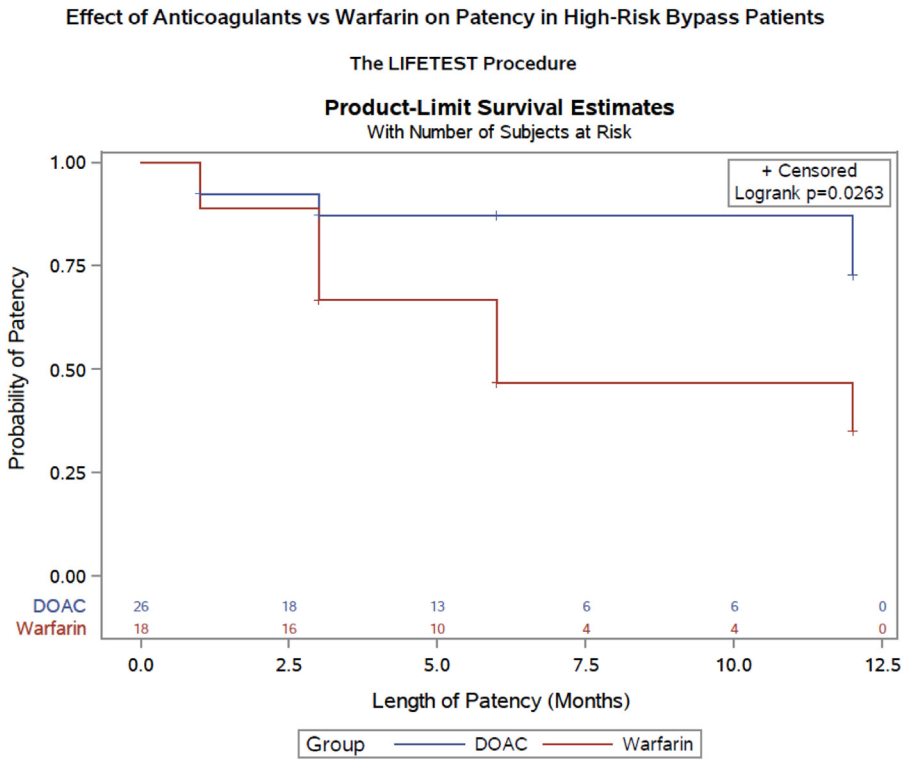

Fig. 1. Kaplan-Meier survival curve patency at 12 months.

Despite research focusing specifically on rivaroxaban as indicated for PAD treatment, physicians have widely adopted the prescription of all DOACs in the said treatment. Additionally, there is limited data comparing the outcomes of DOACs versus warfarin in the treatment of PAD. One prospective, multicenter study, 'Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)' looked at over 9,500 patients receiving either no anticoagulation, a vitamin K antagonist, or a DOAC after peripheral arterial bypasses and found no difference in postoperative outcomes.[11] Of note, over 7,500 patients in BMC2 received no anticoagulation. Our study is a pilot single-institution retrospective study from prospectively collected data that adds to the limited literature on the efficacy of DOACs versus

Table II. Post-operative outcomes and complications

Outcomes	DOAC ($N = 26$) Mean (SD)/%	Warfarin ($N = 18$) Mean (SD)/%	*P*
Follow-Up (Months)	7.2 (6.6)	12.9 (8.6)	**0.030**
Reintervention <30 Days	0.0%	11.1%	0.162
Reintervention >30 Days	23.1%	50.0%	0.106
Cardio/Cerebrovascular Events	7.7%	16.7%	0.386
Bleeding Complications	19.2%	33.3%	0.314
Major Amputation	7.7%	11.1%	1.000
Mortality	0.0%	11.1%	0.162

Bold indicates $P < 0.05$.

warfarin in a particular subset of high-risk bypass patients. Similar to BMC2, we found no difference in the postoperative complications of our HRB patients when it came to anticoagulation choice, but a higher 12-month primary patency rate in patients postoperatively on DOAC compared to warfarin. In proving non-inferior patency rates with use of a DOAC, we can simplify management of thromboembolic patients by decreasing drug-drug interactions, eliminating the need for frequent monitoring of INR levels, and improving patient drug compliance with the intention to increase the lifespan of an HRB.

With regards to comorbidities, there was a significant portion of individuals in the DOAC group who had a history of CAD, as compared to the warfarin group. This finding was interesting, as a study performed by Turgeon et al. showed that monotherapy with a DOAC was not more efficacious in maintaining vessel patency in CAD versus no anticoagulation.[17] However, given the COMPASS trial results, we can assume that more patients have been placed on DOACs recently for CAD and were most likely pre-operatively on the DOAC before their HRB procedure.

This study was limited in its design as a non-randomized comparison between 2 anticoagulant groups in patients with HRB. We were not able to control for the different reasons a patient might have been placed on 1 drug or another, as the decision was largely based on surgeon preference and the anticoagulant choice of the era. Patients followed earlier on in the study were more likely to have been placed on warfarin, compared to patients added later in the study. Prospective randomized controlled trials are needed to further study whether there are any differences in outcomes between using DOACs and warfarin perioperatively in bypass patients.

Another limitation of our study is the sample size that possibly led to an underpowered study. For instance, 65% of patients in the DOAC group were white, compared to 55% of patients in the warfarin group. Although this difference was not statistically significant in our analysis, perhaps with a greater sample size the *P*-value would prove significant. Differences in our patient population compared to the national averages can affect generalizability to the public. Other differences in our patient population included an increased proportion of males compared to females in both groups. Previous studies have shown female sex to be an independent predictor of thromboembolic events.[18,19] Because our study included more men compared to women, our bleeding complication risk rate could be skewed and is a limitation of our study design. Because we are studying this group in an endovascular-oriented era, there are fewer high-risk bypass patients. In our practice, most patients were treated initially with an endovascular approach, and the sample size represents a small subset of patients that failed either failed or were not amenable to endovascular intervention.

A major limitation of our study was our patient's follow-up. Although our outpatient office attempts to contact all patients who miss their scheduled interviews through phone calls and certified letters, many of them, notably the ones in our DOAC group, did not reach the full 12-month follow-up period. When looking at 24-month patency rates between the 2 groups, an initial scan found no significant difference. Follow-up rates tend to drop after the initial few visits if patients are clinically doing well after surgery. Also, when bypass grafts begin to fail, most patients return for medical care. Another factor was the COVID-19 pandemic, which contributed to decreased follow-up. Regardless, given the follow-up rate of this initial cohort, there is a risk of a type I error, and further follow-up is needed to continue monitoring the patency rates of patients who have not reached the 12-month period and to continue monitoring patency past the 12-month period.

CONCLUSION

DOACs have become the standard of care for anticoagulation. In our single-institution pilot study, we found that patients postoperatively on DOACs appeared to have higher graft patency rates than those placed on warfarin. DOACs could be considered as a safe alternative to warfarin in the postoperative period for select patients with HRB. Future large, prospective, and randomized multicenter studies are needed to further examine the relationship between DOACs and warfarin on bypass patency.

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