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ORIGINAL ARTICLE

Outcomes in patients undergoing periprocedural interruption of warfarin or direct oral anticoagulants

Jeffrey Lee[1] | Xiaowen Kong[2] | Brian Haymart[2] | Eva Kline-Rogers[2] | Scott Kaatz[3] | Vinay Shah[3] | Mona A. Ali[4] | Jay Kozlowski[5] | James Froehlich[2] | Geoffrey D. Barnes[2]

[1]University of Michigan Department of Internal Medicine, Frankel Cardiovascular Center, Rush Medical College, Rush University Medical Center, Ann Arbor, Michigan, USA

[2]University of Michigan Department of Internal Medicine, Frankel Cardiovascular Center, Ann Arbor, Michigan, USA

[3]Division of Hospital Medicine, Henry Ford Hospital, Detroit, Michigan, USA

[4]Department of Heart and Vascular Services, Royal Oak, Michigan, USA

[5]DMC Huron Valley-Sinai Hospital, Commerce, Michigan, USA

Correspondence

Jeffrey Lee, University of Michigan Department of Internal Medicine, Frankel Cardiovascular Center, Rush Medical College, Rush University Medical Center, 1425 E Ann St, Ann Arbor, Michigan 48109, USA.
Email: leejeffr@umich.edu

Abstract

Background: Differences in clinical outcomes following a temporary interruption of warfarin or a direct oral anticoagulant (DOAC) for a surgical procedure are not well described. Differences in patient characteristics from practice-based cohorts have not typically been accounted for in prior analyses.

Aim: To describe risk-adjusted differences in postoperative outcomes following an interruption of warfarin vs DOACs.

Methods: Patients receiving care at six anticoagulation clinics participating in the Michigan Anticoagulation Quality Improvement Initiative were included if they had at least one oral anticoagulant interruption for a procedure. Inverse probability of treatment weighting (IPTW) was used to balance baseline differences between the warfarin cohort and DOAC cohort. Bleeding and thromboembolic events within 30 days following the procedure were compared between the IPTW cohorts using the Poisson distribution test.

Results: A total of 525 DOAC patients were matched with 1323 warfarin patients, of which 923 were nonbridged warfarin patients and 400 were bridged warfarin patients. The occurrence of postoperative minor bleeding (10.8% vs. 4.7%, $p < .001$), major bleeding (2.9% vs. 1.1%, $p = .01$) and clinically relevant nonmajor bleeding (CRNMB) (6.5% vs. 3.0%, $p = .002$) was greater in the DOAC cohort compared with the nonbridged warfarin cohort. The rates of postoperative bleeding outcomes were similar between the DOAC and the bridged warfarin cohorts.

Conclusion: Perioperative interruption of DOACs, compared with warfarin without bridging, is associated with a higher incidence of 30-day minor bleeds, major bleeds, and CRNMBs. Further research investigating the perioperative outcomes of these two classes of anticoagulants is warranted.

1 | INTRODUCTION

The direct oral anticoagulants (DOACs), which include apixaban, dabigatran, rivaroxaban, and edoxaban, are now first-line therapy for treatment of venous thromboembolism (VTE) and stroke prevention in atrial fibrillation (AF). Many patients taking chronic anticoagulant therapy will require temporary interruption for a surgical procedure.[1] Management of the anticoagulant in the perioperative period can be complicated because the pharmacokinetic properties of each agent differ, most significantly as compared with warfarin.

Because of its long half-life, warfarin is often interrupted several days before the procedure. For patients with a high risk of thrombotic complications, "bridging" therapy with low molecular weight heparin or other short-acting parenteral anticoagulants are frequently used while the anticoagulant activity of warfarin wanes or returns to therapeutic range. This practice, however, is associated with higher risk of bleeding compared with those in whom bridging therapy was not initiated.[2–4] In contrast to warfarin, DOACs have both a short half-life and rapid onset of action, which make them ideal for perioperative use and removes the necessity of bridging anticoagulation.[5,6] Prior studies have compared postoperative outcomes of patients following the perioperative interruption of DOACs vs. warfarin and found no major differences in postoperative rates of major bleeding or thromboembolic events.[7–10] However, because these were post hoc analyses of clinical trials, the patient samples include a more selective population that is commonly seen in routine clinical practice. Therefore, we aimed to compare 30-day postoperative bleeding and thromboembolic events associated with DOAC versus warfarin management in the perioperative period in a practice-based cohort of patients.

2 | MATERIALS AND METHODS

The Michigan Anticoagulation Quality Improvement Initiative (MAQI[2]) is a Blue Cross Blue Shield of Michigan/Blue Care Network-funded multicenter collaborative of anticoagulation management services in the state of Michigan. MAQI[2] was formed in 2008 with the goal of improving patient safety and outcomes by collecting and comparing patient clinical data, identifying best practices, and conducting quality improvement initiatives. Currently, there are six hospitals in Michigan participating in the program. Patients initiated on either a DOAC or warfarin are randomly selected for entry into the MAQI[2] database and followed longitudinally so long as they remain on therapy and are managed at the participating health system. All data abstractors undergo training, and each center undergoes regular audits to ensure high-quality data collection and agreement with predefined data element definitions. More information about MAQI[2] has been previously described.[11] Institutional review board

> **Essentials**
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> - Few studies adjust for cofounders in 'direct oral anticoagulants (DOAC)' and warfarin cohorts.
> - Inverse probability weighting used to balance covariates between our DOAC and warfarin cohorts.
> - No difference in postoperative adverse events between DOAC cohort vs bridged warfarin cohort.
> - DOAC cohort associated with higher rates of bleeding/thrombosis vs non-bridged warfarin cohort.

approval has been obtained at each site and the coordinating center (University of Michigan).

2.1 | Patient selection

Patients who had a temporary interruption of DOAC or warfarin therapy for an elective surgical procedure were included if they had follow-up for at least 3 months after the procedure. Patients with indications for anticoagulant use other than AF or VTE were excluded.

2.2 | Data collection

Baseline patient information, including demographics, medications, and comorbidities were abstracted from patient charts at the time of anticoagulation initiation. Information about medication changes, new comorbidities, procedures, and bleeding or thrombotic events were abstracted for each patient interaction with the anticoagulation management service for warfarin-treated patients and at regular 6-month follow-up intervals for DOAC-treated patients. Procedural data abstracted from the medical record included the date of procedure, anticoagulation interruption and restart dates, whether or not heparin bridging was used, and the type of procedure. The procedures were categorized into having low or high bleed risk based on categories from the BRIDGE trial.[3]

2.3 | Outcomes

The primary outcomes of our study were 30-day postoperative thromboembolic or bleeding events. Thromboembolic events included the composite of transient ischemic attacks, ischemic stroke, and VTE. Bleeding events were classified into minor bleeds, major bleeds, and clinically relevant nonmajor bleeds (CRNMB). Criteria

for major and CRNMBs were based on International Society on Thrombosis and Haemostasis (ISTH) definitions.[12,13]

2.4 | Statistical analysis

Inverse probability of treatment weighting (IPTW) was used to compare the DOAC and warfarin treatment groups. This statistical method assigns a weight to each patient based on their propensity score, creating a pseudopopulation that allows us to better determine the effects of the two treatments. The IPTW approach allows us to use the entirety of our cohort and maximize the inclusion of as many warfarin-treated and DOAC-treated patients as possible while preserving exact matching for sex, anticoagulation indication, and procedural bleeding risk. Other clinical variables were included in the IPTW, and a standardized difference of less than 0.1 was considered negligible (Appendix S1). Bleeding and thromboembolic risk comparisons were adjusted for the average modified HAS-BLED (excluding time in therapeutic range) scores.[14,15] Following IPTW reweighting, multivariate logistic regression was performed to calculate odds ratios that compared 30-day postoperative outcomes.

3 | RESULTS

3.1 | Study population

Of a total of 14168 warfarin and 3253 DOAC patients in the MAQI[2] registry, 1323 (9%) warfarin-treated and 525 (16%) DOAC-treated patients met inclusion/exclusion criteria for our study (Figure 1). Following IPTW reweighting, differences between the two cohorts were minimal (Appendix S1). Of the warfarin-treated patients, 400 of 1323 (30%) were bridged during the interruption. Compared with the bridged warfarin cohort, the DOAC cohort was significantly older (71.0years vs. 65.7years, $p<.001$), had a higher concomitant rate of hypertension (80.0% vs. 64.0%, $p<.001$), had more cases of remote bleeding (6.5% vs. 3.5%, $p = .04$), were prescribed less antiplatelets (26.5% vs. 41.8%, $p<.001$) and nonsteroidal anti-inflammatory drugs (3.6% vs. 10.0%, $p<.001$), had more bleeding events before the procedure (17.5% vs. 11.2%, $p = .007$), had a higher CHA_2DS_2-VASc score (3.54 vs. 3.12, $p = .001$), had a lower rate of high bleed risk procedures (30.1% vs. 60.3%, $p<.001$), had a higher rate of low bleed risk procedures (69.3% vs. 36.5%, $p<.001$), had a higher proportion of patients being treated for AF (70.7% vs. 35.3%, $p<.001$), were taking their anticoagulant for more days before the procedure (391 vs. 243, $p<.001$), and stopped taking their anticoagulant for more days before the procedure (5 vs. 3, $p<.001$). Compared with the nonbridged warfarin cohort, the DOAC cohort was significantly younger (71.0years vs. 72.4years, $p = .03$), had a lower rate of concomitant abnormal renal function (15.4% vs. 22.1%, $p = .002$), were prescribed fewer antiplatelets (26.5% vs. 43.1%, $p<.001$) and nonsteroidal anti-inflammatory drugs (3.6% vs. 8.3%, $p = .001$), had more bleeding events before the procedure

(20.7% vs. 11.2%, $p<.001$), had a lower modified HAS-BLED score (2.58 vs. 3.01, $p<.001$), and had a lower rate of high bleed risk procedures (30.1% vs. 43.0%, $p<.001$), had a higher rate of low bleed risk procedures (69.3% vs. 54.1%, $p<.001$), were taking their anticoagulant for more days before the procedure (480 vs. 243, $p<.001$), stopped taking their anticoagulant for more days before the procedure (5 vs. 3, $p<.001$), and had a lower procedure to restart interval (0 vs. 1, $p = .002$). No other significant differences in patient characteristics or procedure bleed risk between the groups were found (Table 1A). Thirty-nine bleeding events occurred in patients taking apixaban 5 mg twice daily, and 33 occurred in patients taking rivaroxaban 20mg each day, which were the two dosages with the highest incidence of bleeding events among the DOAC cohort.

3.2 | Postoperative outcomes

Among the 1323 warfarin patients and 525 DOAC patients in the treatment cohorts, 260 bleeding events and 12 thrombotic events were reported. Compared with the nonbridged warfarin cohort, the DOAC cohort had a significantly higher postoperative rate of both minor bleeds (10.8% vs. 4.7%, $p<.001$), major bleeds (2.9% vs. 1.1%, $p = .01$), and CRNMBs (6.5% vs. 3.0%, $p = .002$) (Table 1B). There was no difference in the rate of thromboembolic events between the nonbridged warfarin cohort and the DOAC cohort. Similarly, there was no difference in any bleeding or thromboembolic events between the bridged warfarin cohort and DOAC cohort.

3.3 | IPTW outcomes

Between the nonbridged warfarin cohort and the DOAC cohort, IPTW analysis indicates that DOAC use contributed most greatly to the differences in the rates of minor bleeds (OR 2.546, 95% CI 1.656–3.912), major bleeds (OR 3.712, 95% CI 1.605–8.584), and CRNMBs (OR 2.928, 95% CI 1.718–4.991) (Figure 2).

4 | DISCUSSION

Among the 1323 warfarin patients and 525 DOAC patients who underwent surgical procedure requiring perioperative interruption, rates of minor bleeding, major bleeding, and bleeding requiring an emergency department visit were lower for patients treated with warfarin and no bridging therapy than for DOAC-treated patients following IPTW weighting. There were no differences in thromboembolic events between warfarin-treated patients without bridging and DOAC-treated patients, and no differences between warfarin-treated patients with bridging and DOAC-treated patients. IPTW analysis indicates that DOAC use contributed most greatly to the differences in bleeding rates between the two cohorts.

Given the large body of evidence associating bridging therapy with increased bleeding risk, it was unsurprising that the bridged
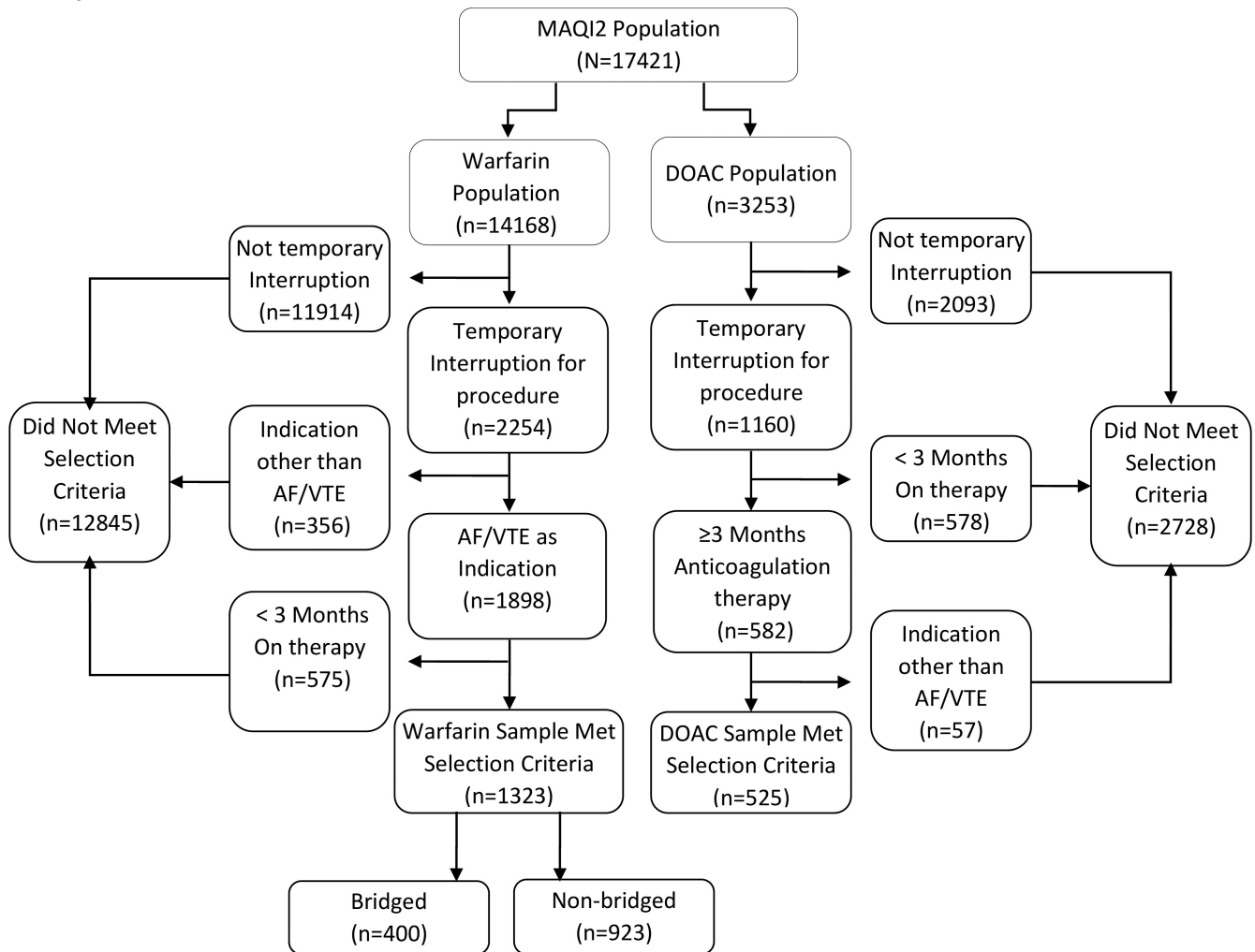
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                    │   MAQI2 Population   │
                    │     (N=17421)       │
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FIGURE 1 Matching procedure diagram

warfarin cohort had a numerically higher bleeding rate than to our unbridged warfarin cohort.[2–4] Our bridged warfarin cohort saw similar outcomes with our DOAC cohort with regard to bleeding and thromboembolic events. In contrast to warfarin, DOACs have both a short half-life and fast onset of action and thus do not require bridging.[16,17] This leads to a shortened time between the surgical procedure and when a DOAC medication is stopped or restarted as compared to warfarin. It is thus not unexpected that the addition of a fast-acting bridging agent in our bridged warfarin cohort to result in similar rates of bleeding compared to our DOAC cohort.

DOAC-treated patients in our study experienced a postoperative major bleed rate of 2.9%, which is slightly higher (2.9% vs. 0.9%–1.85%) than the rates of the cohorts in PAUSE.[18] However, our rate of minor bleeding was 10.8%, which is notably higher than the rates of 4.3%–5.7% of the cohorts of the PAUSE study. Two potential contributing factors why our DOAC cohort had a higher rate of major bleeding are the higher rate of antiplatelet use[19–21] (26.5% vs. 9.1%–14.7%) and a higher modified HAS-BLED score[22–24] (2.6 vs. 1.9).

Shaw and colleagues also performed a retrospective analysis of warfarin and DOAC interruption for surgical procedures. In addition to the multivariable logistic-regression model that they utilized,

we also implemented IPTW before logistic regression to adjust for confounding variables.[25] Their analysis also found that postoperative rates of major bleeding were significantly higher in the warfarin cohort, which we did find in our analysis of our nonbridged warfarin cohort. However, there are various differences between the two studies that led to this shared finding. First, our study included patients whose primary indication for anticoagulation was either AF or VTE, whereas the Shaw study focused on AF only, although our study's IPTW analysis indicates that an indication of AF does not contribute to the differences in bleeding rates in the DOAC versus nonbridged warfarin cohorts (Figure 2). Additionally, we differentiated our warfarin patients into cohorts based on the use of bridging low molecular weight heparin. Last, we used an IPTW statistical approach, which may have resulted in different analysis of the variables and affected outcomes since IPTW sets our groups to be similar in our covariates before logistics regression. Further efforts are needed to reconcile the differences between these two important studies of perioperative anticoagulation care.

The key strength of our study is the use of our IPTW statistical analysis, which is able to account for various potential confounding variables in the warfarin and DOAC cohorts while maintaining

TABLE 1 (A) Patient characteristics and procedure bleed risk of warfarin- and DOAC-matched cohorts. (B) Thirty-day postoperative outcomes

	Warfarin (Bridged) n = 400	Warfarin (Nonbridged) n = 923	DOAC n = 525	p-value Warfarin Bridged vs. DOAC	p-value Warfarin Nonbridged vs. DOAC
(A)					
Age (mean ± SD)	65.7 ± 13.8	72.4 ± 11.7	71.0 ± 12.2	<.001	.03
Sex, n (%), male	198 (49.5)	493 (53.4)	262 (49.9)	.90	.20
Comorbidities, n (%)					
HTN	256 (64)	717 (77.7)	420 (80.0)	<.001	.30
Abnormal renal function	65 (16.3)	204 (22.1)	81 (15.4)	.73	.002
Abnormal hepatic/ liver function	12 (3)	37 (4)	25 (4.8)	.18	.50
TIA/CVA	72 (18)	121 (13.1)	76 (14.5)	.15	.47
Recent bleeding	16 (4)	54 (5.9)	27 (5.1)	.41	.57
Remote bleeding	14 (3.5)	42 (4.6)	34 (6.5)	.04	.11
Medications, n (%)					
Antiplatelets	167 (41.8)	389 (43.1)	139 (26.5)	<.001	<.001
Nonsteroidal anti-inflammatory drugs	40 (10)	77 (8.3)	19 (3.6)	<.001	.001
Recurrent adverse events before procedure, n (%)					
Thrombosis/stroke	8 (2)	10 (1.1)	6 (1.1)	.29	.92
Bleeding	70 (17.5)	191 (20.7)	59 (11.2)	.007	<.001
Risk scores (Mean ± SD)					
TTR	0.65 ± 0.15	0.66 ± 0.14	–	–	–
CHA_2DS_2-VASc	3.12 ± 1.95	3.71 ± 1.69	3.54 ± 1.78	.001	.07
Modified HAS-BLED	2.66 ± 1.43	3.01 ± 1.34	2.58 ± 1.28	.35	<.001
Procedure bleed risk, n (%)					
High/medium	241 (60.3)	397 (43.0)	158 (30.1)	<.001	<.001
Low	146 (36.5)	499 (54.1)	364 (69.3)	<.001	<.001
AF as indication	141 (35.3)	677 (73.4)	371 (70.7)	<.001	.27
Duration of anticoagulation before procedure, median days (IQR)	391 (706)	480 (806)	243 (258)	<.001	<.001
Days from stop to procedure median (IQR)	5 (0)	5 (1)	3 (2)	<.001	<.001
Days from procedure to restart median (IQR)	1 (0, 2)	0 (0, 1)	1 (0, 2)	.80	.002
DOAC dosage at bleed					
Apixaban 2.5 mg twice daily	-	–	9	–	–
Apixaban 5 mg twice daily	–	–	29	–	–
Apixaban 10 mg twice daily	–	–	1	–	–
Dabigatran 150 mg twice daily	–	–	1	–	–
Edoxaban 60 mg every day	–	–	1	–	–

TABLE 1 (Continued)

	Warfarin (Bridged) n = 400	Warfarin (Nonbridged) n = 923	DOAC n = 525	p-value Warfarin Bridged vs. DOAC	p-value Warfarin Nonbridged vs. DOAC
(A)					
Rivaroxaban 15 mg every day	–	–	2	–	–
Rivaroxaban 20 mg every day	–	–	28	–	–
DOAC dosage at clot					
Apixaban 5 mg twice daily	–	–	3	–	–
Edoxaban 60 mg twice daily	–	–	1	–	–

n (%)	Warfarin (Bridged) n = 400	Warfarin (Nonbridged) n = 923	DOAC n = 525	p-value Warfarin Bridged vs. DOAC	p-value Warfarin Nonbridged vs. DOAC
(B)					
Any minor bleeds	34 (8.5)	43 (4.7)	57 (10.8)	.23	<.001
Major bleeds	13 (3.3)	10 (1.1)	15 (2.9)	.73	.01
TIA/stroke/VTE	3 (0.8)	5 (0.5)	4 (0.8)	.98	.61
CRNMBs	26 (6.5)	28 (3)	34 (6.5)	.99	.002

Abbreviations: AF, atrial fibrillation; CRNMB, clinically relevant nonmajor bleeding; CVA, cardiovascular accident; DOAC, direct oral anticoagulant; HTN, hypertension; IQR, interquartile range; TIA, transient ischemic accident; TTR, time in therapeutic range.
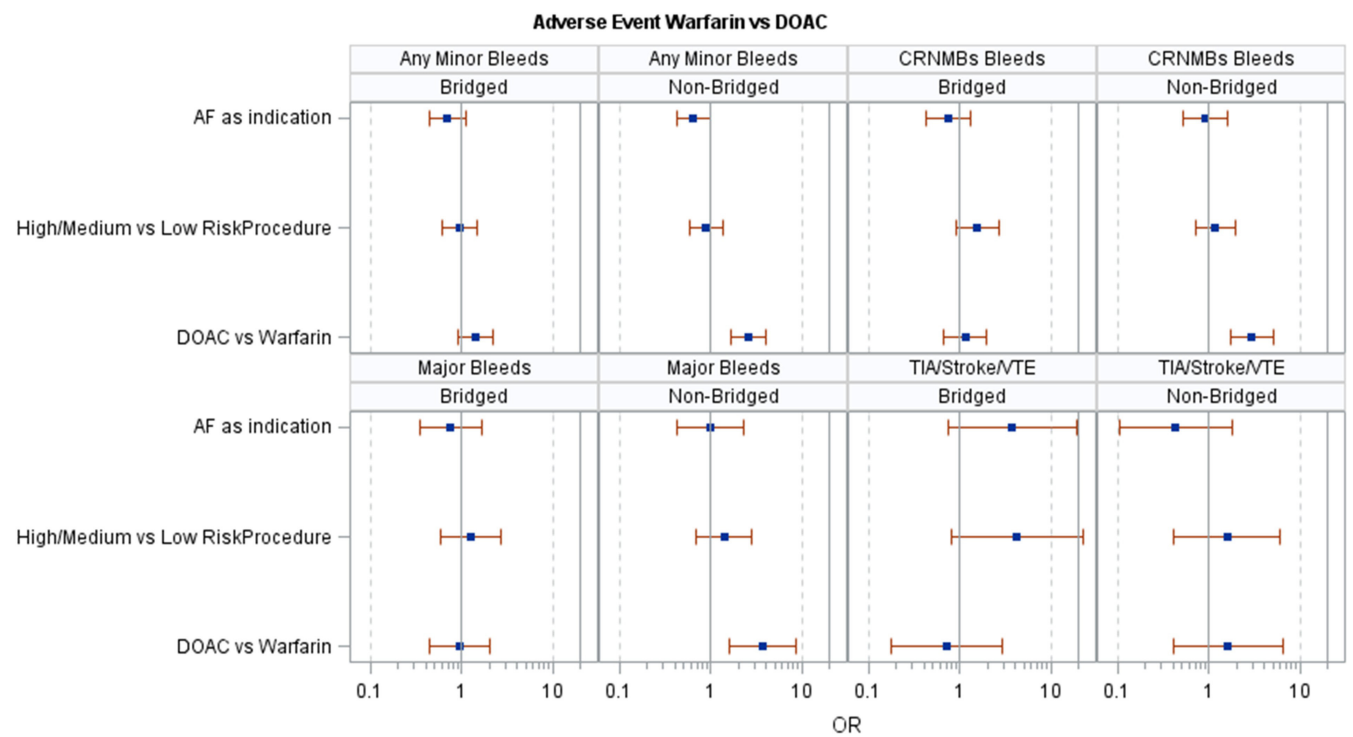

FIGURE 2 Inverse probability of treatment weighting outcomes

statistical power and generalizability. This approach was not taken with most other studies comparing DOAC and warfarin outcomes in the perioperative period.[7–10] Although each of those analyses were conducted on randomized, controlled trial populations and thus reduce the effect of confounding variables on outcomes, the samples for these studies are limited to patients who are eligible for randomization. In contrast, our data were not limited to patients eligible for randomization, therefore representing a potentially more

generalizable estimate of adverse event rates. Last, our analysis distinguishes between warfarin-treated patients into both a bridged and a nonbridged cohort, which is critical given the strong evidence associating use of bridging therapy with increased bleeding risk.[2–4]

Despite these strengths, certain limitations must be acknowledged. First, the modest sample sizes and inclusion of patients from one geographic region may limit generalizability. Second, data on exact perioperative management of DOACs was not available for this analysis. Therefore, it is unclear whether our DOAC perioperative interruption practices are fully consistent with the PAUSE protocol. Third, as with any retrospective cohort study, our analysis is only as accurate as what is depicted in our electronic health records and cannot account for things such as misinformation or lapses in data. Fourth, although the use of IPTW methodology significantly reduces the impact of confounding in the analysis, covariate balance between the two groups are notably different before and after the probability weighting is applied. Fifth, data on the rationale for why bridging was or was not given were not available in the MAQI[2] dataset. Sixth, we do not have data on the use of prophylactic-dose heparin in the periprocedural period. Seventh, we are only able to comment on association, not causation. Last, although we used a fairly comprehensive list of confounding variables for our matching procedure, it is possible that there are other confounding factors that were not included and influenced our results.

5 | CONCLUSION

Our study suggests that the periprocedural interruption of DOACs may be associated with a higher incidence of 30-day minor bleeds, major bleeds, and bleeds requiring medical therapy when compared with the interruption of nonbridged warfarin. However, no difference in bleeding or thromboembolic events was noted between patients with warfarin who received bridging therapy and DOAC-treated patients. Further studies that investigate the effects of perioperative interruption of DOACs and warfarin on postoperative outcomes while addressing potential issues of confounding variables are warranted.

AUTHOR CONTRIBUTIONS

J. Lee: conceived the project, reviewed analyses, and drafted the manuscript. X. Kong: conducted analyses and critically reviewed the manuscript. B. Haymart: conceived the project, reviewed analyses, and critically reviewed the manuscript. G. Barnes: conceived the project, reviewed analyses, and critically reviewed the manuscript. All other authors critically reviewed the manuscript.

CONFLICT OF INTEREST

ORCID

Jeffrey Lee https://orcid.org/0000-0001-6906-2638
Xiaowen Kong https://orcid.org/0000-0003-4548-3600
Brian Haymart https://orcid.org/0000-0001-8484-6393
Scott Kaatz https://orcid.org/0000-0002-3080-3328
Vinay Shah https://orcid.org/0000-0001-8489-3675
Mona A. Ali https://orcid.org/0000-0003-2416-6702
Jay Kozlowski https://orcid.org/0000-0002-7950-0096
James Froehlich https://orcid.org/0000-0003-2327-8235
Geoffrey D. Barnes https://orcid.org/0000-0002-6532-8440

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.