

## Full Length Article

## Comparison of temporary interruption with continuation of direct oral anticoagulants for low bleeding risk procedures

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## ABSTRACT

**Introduction:** Limited data is available on the rates of bleeding and thromboembolic events for patients undergoing low bleeding risk procedures while taking direct oral anticoagulants (DOAC).

**Methods:** Adults taking DOAC in the Michigan Anticoagulation Quality Improvement Initiative (MAQI<sup>2</sup>) database who underwent a low bleeding risk procedure between May 2015 and Sep 2019 were included. Thirty-day bleeding (of any severity), thromboembolic events, and death were compared between DOAC temporarily interrupted and continued uninterrupted groups. Adverse event rates were compared using an inverse probability weighting propensity score.

**Results:** There were 820 patients who underwent 1412 low risk procedures. DOAC therapy was temporarily interrupted in 371 (45.2%) patients (601 [42.6%] procedures) and continued uninterrupted in 449 (54.8%) patients (811 [57.4%] procedures). DOAC patients with temporary interruptions were more likely to have diabetes, prior stroke or TIA, prior bleeding, higher CHA<sub>2</sub>DS<sub>2</sub>-VASc, and higher modified HAS-BLED scores. DOAC interruption was common for gastrointestinal endoscopy, electrophysiology device implantation, and cardiac catheterization while it was less common for cardioversion, dermatologic procedures, and subcutaneous injection. After propensity score adjustment, bleeding risk was lower in the DOAC temporary interruption group (OR 0.62, 95% CI 0.41–0.95) as compared to the group with continuous DOAC use. Rates of thromboembolic events and death did not differ significantly between the two groups.

**Conclusions:** DOAC-treated patients undergoing low bleeding risk procedures may experience lower rates of bleeding when DOAC is temporarily interrupted. Prospective studies focused on low bleeding risk procedures are needed to identify the safety DOAC management strategy.

### 1. Introduction

Atrial fibrillation (AF) and venous thromboembolism (VTE) are major health problems in the United States with an estimated 1.2 million cases of AF in 2010 and 1 million VTE events occurring in 2014 alone [1]. Anticoagulation used in these patients to prevent thromboembolic complications also increases the risk of bleeding [2]. Since 2009, the

direct oral anticoagulants (DOAC) have gained prominence and are now increasingly used as compared to warfarin [3].

In preparation for surgical or invasive procedures, patients often require a temporary interruption of the anticoagulant to reduce peri-procedural bleeding risk [4]. For certain lower bleeding risk procedures, such as pacemaker implantation or ablation of atrial fibrillation, randomized trial data in both warfarin- and DOAC-treated patients

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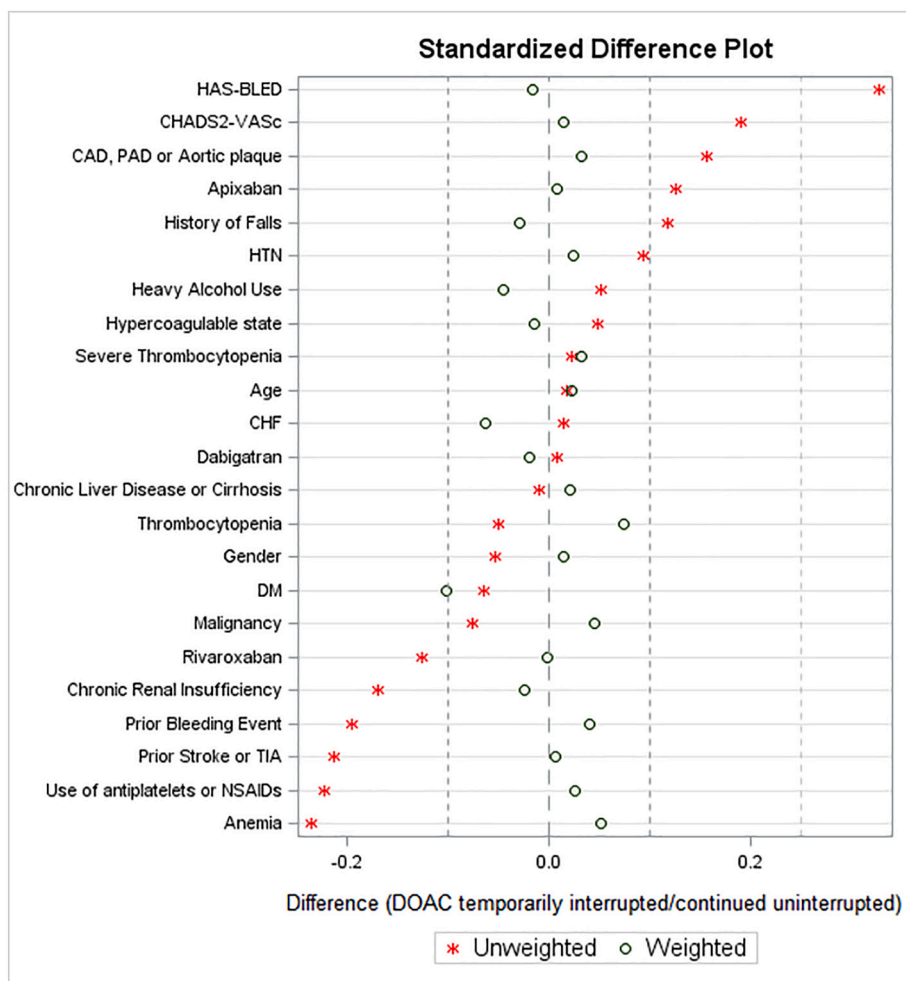


Fig. 1. Standardized difference plot before and after inverse probability weighting.

suggests safety and efficacy when the anticoagulant is continued uninterrupted [5–11]. While peri-procedural anticoagulation management for electrophysiology (EP) procedures has been fairly well studied, limited data is available to compare temporary interruption versus routine continuation of DOAC medications for other low bleeding risk procedures. We aimed to describe rates of bleeding and thromboembolic events for patients undergoing low bleeding risk procedures while taking DOAC medications.

## 2. Methods

Patients taking DOAC therapy were identified from four hospitals participating in the Michigan Anticoagulation Quality Improvement Initiative (MAQI<sup>2</sup>). MAQI<sup>2</sup> is a Blue Cross Blue Shield of Michigan/Blue Care Network (BCBSM/BCN)-funded collaborative of hospitals- or group practice-affiliated anticoagulation services across the state of Michigan. Beginning in 2015, patients initiated on DOAC therapy at a participating MAQI<sup>2</sup> center were eligible for enrollment in the MAQI<sup>2</sup> database. Patients were randomly selected monthly for enrollment into the registry. During the study period, MAQI<sup>2</sup> had no impact on anticoagulant management decisions, which were made by the primary providers. Data abstractors undergo standardized training and participating sites undergo regular audits to ensure that abstracted data is accurate and concordant with pre-set clinical definitions. Major clinical events (including stroke, systemic embolism and major bleeding events) undergo audit by the coordinating center. Use of the MAQI<sup>2</sup> registry is approved with a waiver of informed consent by the Institutional Review

Boards at the University of Michigan (coordinating center) and at each participating site. [12–14]

### 2.1. Patient selection

From the MAQI<sup>2</sup> DOAC registry, we identified adult patients taking DOAC medications at the four participating sites who underwent a low bleeding risk procedure between May 2015 to September 2019. Low bleeding risk procedures included: biopsy (e.g. bone marrow, thyroid, endometrial), bronchoscopy, cardiac ablation, cardiac catheterization, cardioversion, cutaneous incision and drainage, cystoscopy, dental procedure, dermatologic procedure, electrophysiology device implantation, gastrointestinal (GI) endoscopy, ophthalmologic procedure, peripherally inserted central catheter placement, port placement/removal, subcutaneous injection, and other surgery/procedure lasting <1 h (procedures not categorized into any of the previous groups with duration less than 1 h). This criteria was initially developed based on similar criteria used in the BRIDGE (Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation) trial [15].

Patients on heparin or low molecular weight heparin (LMWH) bridging, and those undergoing moderate- or high-bleeding risk procedure were excluded.

### 2.2. Data collection

Since patients may undergo multiple procedures with different peri-procedural anticoagulation management for each procedure, analysis

**Table 1**  
Demographic comparison between DOAC temporarily interrupted and continued uninterrupted groups.

Demographics	DOAC temporarily interrupted N = 371	DOAC continued uninterrupted N = 449	Standardized difference	
			Unweighted	Unweighted
Age	69.9 ± 12.6	69.7 ± 12.8	0.0166	0.0166
Male Gender	206 (55.5%)	255 (56.8%)	−0.0543	−0.0543
Hypertension	284 (76.6%)	334 (74.4%)	0.0936	0.0936
Heart Failure	84 (22.6%)	94 (20.9%)	0.0139	0.0139
Diabetes Mellitus	112 (30.2%)	101 (22.5%)	−0.0650	−0.0650
Prior Stroke or TIA	64 (17.3%)	43 (9.6%)	−0.2129	−0.2129
CAD, PAD or Aortic plaque	122 (32.9%)	129 (28.7%)	0.1555	0.1555
Chronic Liver Disease or Cirrhosis	20 (5.4%)	22 (4.9%)	−0.0108	−0.0108
Chronic Renal Insufficiency	65 (17.5%)	56 (12.5%)	−0.1692	−0.1692
Heavy Alcohol Use	28 (7.6%)	31 (6.9%)	0.0516	0.0516
Malignancy	115 (31.0%)	138 (30.7%)	−0.0762	−0.0762
Thrombocytopenia <sup>a</sup>	44 (11.9%)	54 (12.0%)	−0.0510	−0.0510
Severe Thrombocytopenia <sup>b</sup>	2 (0.54%)	4 (0.89%)	0.0220	0.0220
Anemia <sup>c</sup>	150 (40.4%)	112 (25.1%)	−0.2365	−0.2365
Prior Bleeding Event	186 (50.1%)	150 (33.4%)	−0.1955	−0.1955
History of Falls	47 (12.7%)	44 (9.8%)	0.1174	0.1174
Bleeding diathesis	0	2 (0.45%)	–	–
Hypercoagulable state	5 (1.4%)	6 (1.3%)	0.0478	0.0478
Drugs <sup>d</sup>	130 (35.0%)	129 (28.7%)	−0.2234	−0.2234
CHA <sub>2</sub> DS <sub>2</sub> -VASC score	3.5 ± 1.9	3.2 ± 1.8	0.1895	0.1895
Modified HAS-BLED Score	2.8 ± 1.4	2.4 ± 1.2	0.3271	0.3271
Apixaban	258 (69.6%)	289 (64.4%)	0.1253	0.1253
Rivaroxaban	107 (28.8%)	154 (34.3%)	−0.1256	−0.1256
Dabigatran	6 (1.6%)	5 (1.1%)	0.0081	0.0081
Edoxaban	0	1 (0.22%)	–	–

Abbreviations: TIA = transient ischemic attack; CAD = coronary artery disease; PAD = peripheral arterial disease; NSAIDs = nonsteroidal anti-inflammatory drugs; CHA<sub>2</sub>DS<sub>2</sub>-VASC = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category; HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile INR (excluded), elderly, drugs or alcohol.

<sup>a</sup> Platelet count of <150,000/L.

<sup>b</sup> Platelet count of <50,000/L.

<sup>c</sup> Hemoglobin <13 g/dL for Men and < 12 g/dL for Women.

<sup>d</sup> Use of aspirin, clopidogrel, prasugrel, ticagrelor or NSAIDs.

was based on the procedure- rather than the patient-level. Procedures were categorized based on DOAC management, namely if DOAC medications were temporarily interrupted or continued uninterrupted. This information is obtained by data abstractors during chart review. The decision of peri-procedural interruption or continuation was made by the primary providers, typically without input from the anticoagulation clinic or research team. Therefore, no details about reasons for DOAC interruption or continuation are available for analysis.

Determination of continuation or interruption of DOAC was made by reviewing all available provider notes in the electronic medical record. We defined interruption as at least one missed dose of DOAC prior to procedure. If periprocedural anticoagulation management was not clear after thorough chart review, the DOAC status around the procedure was recorded as “unknown”. The procedures for which DOAC continuation or interruption was unknown were excluded. Of the 2259 total procedures in the database, 239 had unknown DOAC continuation or interruption status which were excluded. Of the 2020 total procedures with known DOAC status 1412 were low-risk procedures.

### 2.3. Outcomes

Thirty-day bleeding events, thromboembolic events, and death were compared between the interrupted and uninterrupted groups. All events were abstracted from the medical chart by trained abstractors using pre-specified data forms and definitions. Bleeding was characterized as major, clinically relevant non-major (CRNM), or minor according to the International Society of Thrombosis and Hemostasis (ISTH) consensus definitions [16,17]. Bleeding events of any severity (major, minor and CRNM) were grouped and reported as ‘any bleeding.’ Stroke and systemic embolism were defined according to physician diagnosis or discharge diagnosis and abstracted into the registry.

### 2.4. Statistical analysis

For baseline group comparisons, standardized differences were used (Fig. 1) Adverse events were compared by Poisson test and reported as 95% confidence interval (CI) of difference. To adjust for measured potential confounders, we used an inverse probability weighted regression adjustment approach. A propensity model with clinical and demographic elements listed in Table 1 and Fig. 1 was used to calculate inverse probability weight in two groups, namely diabetes, prior stroke or TIA, renal disease, anemia, prior bleeding event, drug use (aspirin, clopidogrel, prasugrel, ticagrelor or NSAIDs) and procedure type, and modified HAS-BLED score [18] [without labile INR (International Normalized Ratio)]. A logistic model was performed based on inverse probability weights, to model outcomes adjusted by significant clinical and demographic elements. Results were reported as odds ratio with their 95% confidence intervals. Standardized weights before adjustment and after inverse probability weighting are shown in Fig. 1. A two-sided  $P < 0.05$  was considered statistically significant for all analyses. Analyses were performed with statistical software SAS version 9.4 (Cary, NC) and R version 3.3.1.

### 3. Results

There were 820 patients who underwent 1412 low risk procedures. Atrial fibrillation was indication for anticoagulation for the majority: 1069 AF, 278 VTE, and 1 for AF and VTE. DOAC therapy was temporarily interrupted in 371 (45.2%) patients (601 [42.6%] procedures) and continued in 449 (54.8%) patients (811 [57.4%] procedures). Apixaban, rivaroxaban, dabigatran and rivaroxaban were the DOAC medications included.

As shown in Table 1, procedures where a patient’s DOAC was temporarily interrupted were more likely to occur in patients with

**Table 2**  
DOAC interruption and continuation for each procedure.

Procedure	Total	DOAC temporarily interrupted		DOAC continued uninterrupted	
		N (%)	Bleeding N (%)	N (%)	Bleeding N (%)
Gastrointestinal endoscopy	264	223 (84.50)	19 (8.52)	41 (15.50)	2 (4.88)
Permanent pacemaker or internal defibrillator insertion or loop recorder	53	42 (79.20)	7 (16.67)	11 (20.80)	1 (9.09)
Cardiac catheterization	105	83 (79.00)	6 (7.23)	22 (21.00)	4 (18.18)
Cardiac Ablation	138	85 (61.60)	9 (10.59)	53 (38.40)	3 (5.66)
Dental surgery or other dental procedure	24	14 (58.33)	1 (7.14)	10 (41.67)	2 (20)
Incision and Drainage	7	4 (57.14)	0	3 (42.86)	1 (33.33)
Port placement/removal	10	5 (50.00)	2 (40)	5 (50.00)	0
Dilation and Curettage	2	1 (50.00)	0	1 (50.00)	0
Any other surgery or procedure lasting less than 1 h	154	74 (48.10)	4 (5.41)	80 (51.90)	6 (7.5)
Biopsy (e.g. bone marrow, thyroid, endometrial)	19	9 (47.37)	1 (11.11)	10 (52.63)	1 (10)
Cataract removal or other ophthalmologic procedure	72	15 (20.80)	3 (20)	57 (79.20)	0
Injection (e.g. cortisone, dermatologic)	80	13 (16.30)	0	67 (83.80)	1 (1.49)
Dermatologic surgery or other dermatologic procedure	129	17 (13.20)	3 (17.65)	112 (86.80)	11 (9.82)
Scoping (e.g. bronchoscopy, nasopharyngeal, knee, cystoscopy)	40	5 (12.50)	0	35 (87.50)	5 (14.29)
Cardioversion	313	9 (2.9)	1 (11.11)	304 (97.10)	14 (4.61)

diabetes (30.2% vs 22.5%), prior stroke or transient ischemic attack (17.3% vs 9.6%), anemia (40.4% vs 25.1%), prior bleeding (50.1% vs 33.4%) and higher modified HAS-BLED scores ( $2.8 \pm 1.4$  vs  $2.4 \pm 1.2$ ). Patients with procedures where DOAC therapy was temporarily interrupted also had higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ( $3.5 \pm 1.9$  vs  $3.2 \pm 1.8$ ). Use of different DOAC agents (apixaban, rivaroxaban, dabigatran and edoxaban) was similar in both groups: apixaban 69.6% vs 64.4% (p 0.12), rivaroxaban 28.8% vs 34.3% (p 0.09), dabigatran 1.6% vs 1.1% (p 0.56) and edoxaban 0% vs 0.22% respectively.

Procedures for which DOAC therapy was most likely to be temporarily interrupted included gastrointestinal (GI) endoscopy (223/263, 84.5%), electrophysiology (EP) device implantation (42/53, 79.2%) and cardiac catheterization (83/105, 79%). Procedures where DOAC was most likely to be continued uninterrupted included cardioversion (304/313, 97.1%), dermatologic procedures (112/129, 86.8%) and subcutaneous injection (67/80, 83.8%) (Table 2).

A small proportion were on low-dose DOAC (defined as rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily). Out of total 820 patients 64 (7.8%) were taking low-dose DOAC medication; the corresponding numbers in the DOAC temporarily interrupted group were 29/371 (7.8%) and in the DOAC continued uninterrupted group 35/449 (7.8%). At the procedure level also a small percentage were on low-dose DOAC: 105/1412 (7.4%) for all procedures, 50/601 (8.3%) for procedures were DOAC was temporarily interrupted and 55/811 (6.8%) when DOAC was

**Table 3**  
Low dose DOAC use.

	Total	DOAC temporarily interrupted	DOAC continued uninterrupted
Patient level (number of patients)	820	371	449
On Low-dose DOAC <sup>a</sup>	64 (7.8%)	29 (7.8%)	35 (7.8%)
Procedure level (number of procedures)	1412	601	811
On Low-dose DOAC <sup>a</sup>	105 (7.4%)	50 (8.3%)	55 (6.8%)

<sup>a</sup> Rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily.

**Table 4**  
Unadjusted outcomes.

Outcomes (30 days post-procedure)	DOAC temporarily interrupted N = 601	DOAC continued uninterrupted N = 811	p-Value
<b>Primary</b>			
Any bleeding events	56 (9.3%)	51 (6.3%)	0.03
Major bleed	9 (1.50%)	4 (0.49%)	0.05
Minor bleed	47 (7.82%)	47 (5.80%)	0.13
CRNM bleed <sup>a</sup>	19 (3.16%)	15 (1.85%)	0.11
Any thromboembolic events	3 (0.50%)	4 (0.49%)	1
<b>Secondary</b>			
Death due to any cause	5 (0.83%)	2 (0.25%)	0.14

CRNM = clinically relevant non-major.

<sup>a</sup> minor bleeds that resulted in ED visits/hospitalizations.

continued uninterrupted (Table 3).

Unadjusted analysis showed that procedures where a patient temporarily interrupted DOAC therapy experienced more 30-day bleeding events and higher incidence of death without a statistically significant difference in thromboembolic events as compared to procedures with continued DOAC use (Table 4). In adjusted analyses, the risk of bleeding decreased when DOAC therapy was temporarily interrupted (OR 0.59, 95% CI 0.39–0.91), while risk of thromboembolic events (OR 1.31, 95% CI 0.26–6.85) and death (OR 0.29, 95% CI 0.04–2.26) showed no statistically significant difference in the two treatment groups. (Fig. 2).

#### 4. Discussion

In this retrospective cohort study of peri-procedural DOAC management in low bleeding risk procedures, temporary interruption of DOAC medications compared to uninterrupted DOAC therapy showed slightly decreased risk of any bleeding.

The largest study of head-to-head comparison of peri-procedural DOAC interruption vs continuation is the BRUISE CONTROL-2 which studied patients undergoing cardiac electrophysiology procedures [11]. Their rates of bleeding (hematoma) of around 5% for all hematomas and 2% for device pocket hematoma in both groups were lower than ours (9% and 6%). A sub-study of the ARISTOTLE trial (apixaban vs. warfarin for atrial fibrillation) reported on perioperative bleeding when apixaban was continued uninterrupted. The most common procedures included were somewhat similar to those we studied. Major bleeding occurred in 28 of 1752 (1.6%) of patients operated on when apixaban was continued uninterrupted [19]. These both differ somewhat from the findings in our study, which demonstrated lower bleeding risk when DOAC therapy is temporarily interrupted. Both these studies focused on EP procedures for atrial fibrillation whereas we included a wide variety of low bleeding risk procedures (also including EP procedures) that is likely responsible for the differing results. Moreover, due to unselected population of DOAC-treated patients, and the retrospective data collection we likely

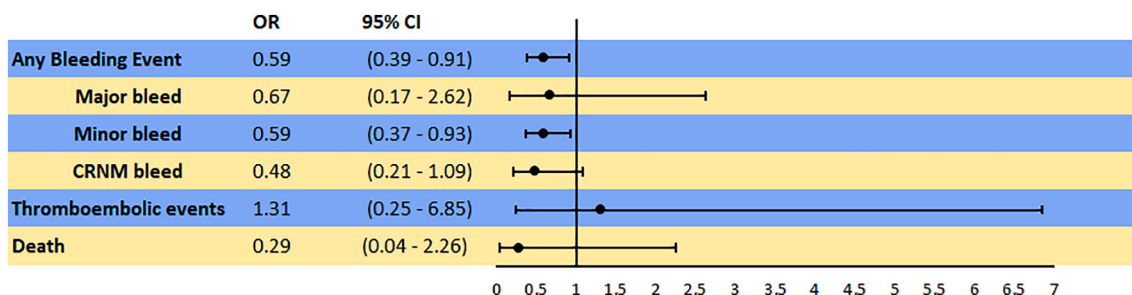


Fig. 2. Inverse probability weighting-adjusted outcomes among DOAC temporarily interrupted vs. continued uninterrupted patients.

had a more heterogeneous patient population which also may explain why our findings are different.

In our study, DOAC therapy was most likely to be temporarily interrupted for GI endoscopy, EP device implantation, and cardiac catheterization procedures. Risk of bleeding from a potential biopsy during endoscopy and use of heparin during cardiac catheterization likely explain the inclination to interrupt DOAC. However, temporary interruption of DOAC therapy for EP device procedures is somewhat surprising given the robust evidence in favor of uninterrupted continuation [5,7–11]. One potential explanation is that with limited DOAC experience and lack of trust or availability in DOAC-specific reversal agents, many clinicians will prefer to stop DOAC therapy and instead initiate heparin. Some patients take low-dose direct oral anticoagulants for long-term venous thromboembolism prevention and providers might be more comfortable continuing this level of anticoagulation versus full therapeutic dose surrounding low-risk procedures. We found that a small percentage and similar number were on low-dose DOAC in both groups at both patient and procedure level, hence it is not likely to be related to the outcomes.

The recent PAUSE study (Perioperative Anticoagulation Use for Surgery Evaluation) demonstrated relative safety and efficacy for a simple perioperative DOAC interruption and resumption protocol for patients undergoing elective procedures, which span the bleeding risk spectrum from low to high [20]. Unlike this study we did not include high bleeding risk procedures in our analysis. However, the low bleeding risk procedures in PAUSE included common gastrointestinal procedures (e.g., colonoscopy), cardiac procedures (e.g., permanent pacemaker implantation or battery change, coronary artery angiography), dental procedures, skin procedures, and eye procedures. These low-risk procedures largely overlapped with those included in our study. Given our observation that routine continuation of DOAC medications (compared to temporary interruption) was associated with increased bleeding risk, a standardized approach to temporary interruption of DOAC medications when patients undergo low bleeding risk procedures may be useful. This warrants further investigation in a prospective study.

An important strength of our study is that the MAQI<sup>2</sup> cohort comprises contemporary real-world patients receiving care in a variety of anticoagulation clinics in both suburban and urban settings, and therefore represents typical patients on anticoagulation in the community. Unlike administrative databases relying on diagnostic and billing codes, our data is manually abstracted by trained personnel and independently audited to verify accurate assessment of comorbidities and events. MAQI<sup>2</sup> auditing ensures highly reliable data abstraction with few patients lost to follow up. The study also has several limitations. As with all retrospective studies, the effect of unmeasured confounding cannot be ruled out even after the use of propensity score methods. Additionally, some adverse outcomes may not have been captured by our registry, especially if patients presented to a different health care system. However, if any adverse event was noted in their medical chart, even in follow up with a primary care provider or other specialist, those events would be identified and abstracted into the MAQI<sup>2</sup> registry.

### 5. Conclusions

DOAC-treated patients undergoing low bleeding risk procedures may have increased bleeding risk when DOAC therapy is continued uninterrupted as compared to when it is temporarily interrupted.

### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AUTHOR	FINANCIAL INTERESTS OR PERSONAL RELATIONSHIPS
Muhammad Adil Sheikh	None
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