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Authors
O'Brien, Emily C
Holmes, DaJuanicia N
Thomas, Laine
et al.

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Therapeutic Strategies Following Major, Clinically Relevant Nonmajor, and Nuisance Bleeding in Atrial Fibrillation: Findings From ORBIT-AF

Emily C. O'Brien, PhD; DaJuanicia N. Holmes, MS; Laine Thomas, PhD; Gregg C. Fonarow, MD; Peter R. Kowey, MD; Jack E. Ansell, MD; Kenneth W. Mahaffey, MD; Bernard J. Gersh, MB, ChB, DPhil; Eric D. Peterson, MD, MPH; Jonathan P. Piccini, MD, MHS; Elaine M. Hylek, MD, MPH

Background—Oral anticoagulation (OAC) reduces stroke risk in atrial fibrillation, but bleeding is a frequent side effect. The decision to discontinue or modify medication regimens in response to a bleeding event may differ according to bleeding site and severity.

Methods and Results—We used data from a large, national outpatient registry, ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; 2010–2011), to evaluate event characteristics and OAC management following the first bleeding event occurring during follow-up. Bleeding events were classified into 3 categories: (1) International Society of Thrombosis and Hemostasis major bleeding, (2) clinically relevant nonmajor bleeding requiring medical attention, and (3) nuisance bleeding not requiring medical attention (eg, bruising, hemorrhoidal bleeding). Of 9743 patients enrolled in ORBIT-AF with follow-up data, 510 (3.23/100 subject-years) experienced a major bleed, 615 (3.90/100 subject-years), experienced a clinically relevant nonmajor bleed, and 1558 (9.87/100 subject-years) experienced a nuisance bleed, among first bleeds over 2 years. Nearly one third of patients (31.6%) discontinued OAC therapy following a major bleeding event, 12.7% following a clinically relevant nonmajor bleed, and 4.5% following a nuisance bleed. Compared with those who experienced a clinically relevant nonmajor or nuisance bleed, patients who experienced a major bleed were more likely to be black and female and to have a history of heart failure and stroke. Those who discontinued were more likely to have central nervous system or gastrointestinal bleeding than those who persisted on OAC therapy.

Conclusions—Overall, 1 in 3 patients who experienced a major bleed was no longer anticoagulated after the event. Those who discontinued OAC were more likely to have central nervous system or gastrointestinal bleeding than those who persisted on OAC. **(*J Am Heart Assoc.* 2018;7:e006391. DOI: 10.1161/JAHA.117.006391.)**

Key Words: anticoagulation • atrial fibrillation • bleeding • risk stratification

Antithrombotic therapy substantially reduces the risk of thromboembolic stroke associated with atrial fibrillation (AF).[1–5] Antithrombotic use for stroke prophylaxis in AF is associated with increased risk of major bleeding, with 1-year major bleeding risk ranging from 2% to 4% in anticoagulated AF patients.[6,7] Although bleeding end points have been extensively examined in randomized clinical trials, contemporary patterns of major, clinically relevant nonmajor (CRNM), and nuisance bleeding have not been fully characterized in outpatient AF populations. Furthermore, current guidelines recommend a risk-stratified approach to bleeding management for patients on oral anticoagulation (OAC) therapy, with distinct pathways depending on the severity of the bleed.[8] However, the decision to discontinue or modify

From the Duke Clinical Research Institute, Durham, NC (E.C.O., D.N.H., L.T., E.D.P., J.P.P.); UCLA Division of Cardiology, Los Angeles, CA (G.C.F.); Jefferson Medical College, Philadelphia, PA (P.R.K.); Lenox Hill Hospital, New York, NY (J.E.A.); Stanford University School of Medicine, Stanford, CA (K.W.M.); Mayo Clinic College of Medicine, Rochester, MN (B.J.G.); Boston University School of Medicine, Boston, MA (E.M.H.).

Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/7/12/e006391/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Emily C. O'Brien, PhD, 2400 Pratt Street, Room 0311 Terrace Level, Durham, NC 27705. E-mail: emily.obrien@duke.edu

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Clinical Perspective

What Is New?

- Among patients with atrial fibrillation, one third discontinue anticoagulation following a major hemorrhage.
- Although lower, discontinuation following a clinically relevant nonmajor bleed (12.7%) or nuisance bleed (4.5%) remains common.

What Are the Clinical Implications?

- Given the known severity of ischemic strokes related to atrial fibrillation, an understanding of the factors driving discontinuation of anticoagulation among patients with high stroke risk is needed.

medication regimens in response to a major bleeding event may differ by the site and severity of the bleed and by patient characteristics. We characterized clinical management patterns of 3 types of bleeding events—major, CRNM, and nuisance bleeding—among patients in ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), a prospective multicenter study of incident and prevalent AF.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

The data source for this analysis was ORBIT-AF, a prospective, US-based outpatient registry of AF. The study design of ORBIT-AF has been published previously.[9] In brief, patients aged ≥18 years were enrolled at 176 clinical sites that were selected to ensure representation from a geographically diverse set of providers and multiple specialties, including cardiology, electrophysiology, and primary care. Clinical information, including demographics, medical comorbidities, AF history, procedures, medications, and provider characteristics, is entered into a web-based form. At ≈6-month intervals, data are prospectively collected on medications, procedures, hospitalizations, disease progression, and vital status for a 2-year period following initial enrollment. Study coordination and management are provided by the Duke Clinical Research Institute.

Between June 2010 and August 2011, 10 135 patients were enrolled in ORBIT-AF (last follow-up date: November 2014). For all analyses, we excluded patients without follow-up data (n=392), patients who did not experience a bleed (n=6514), patients not on OAC before the bleeding event (n=539), patients without treatment data before or after the bleeding event (n=2), or patients on >1 antithrombotic medication before or after the bleed (n=5). Information from the medical record was used to classify patients into major, clinically relevant nonmajor, or nuisance bleeding. We used the first event occurring during the follow-up period. Critical-site bleeding included intracranial, intraocular, intra-articular, intramuscular with compartment syndrome, intraspinal, pericardial, or retroperitoneal bleeding. Major bleeding was defined as any bleeding event meeting International Society of Thrombosis and Hemostasis (ISTH) major bleeding criteria at any point during follow-up.[10] The final study population included 510 participants with major bleeding, 615 with clinically significant nonmajor bleeding, and 1558 with nuisance bleeding (Figure).

Study End Points

The primary outcome of interest for this study was discontinuation of OAC (warfarin, dabigatran, rivaroxaban, apixaban) as reported at the first clinic visit following a bleeding event. Because ORBIT follow-up visits took place every 6 months, we evaluated discontinuations in the first 6 months after a bleeding event occurred. Discontinuations were identified for any patient who did not report being on OAC or who reported a discontinuation of medication. A secondary outcome was the antithrombotic treatment pattern after the bleeding event, which was ascertained by comparing medication information at the most proximal visits before and after the bleeding event. For this analysis, we evaluated switching between OAC and antiplatelet therapy (prasugrel, clopidogrel, ticagrelor, or aspirin); triple therapy (OAC plus antiplatelet therapy [prasugrel, clopidogrel, or ticagrelor] and aspirin); and dual antiplatelet therapy (prasugrel, clopidogrel, or ticagrelor, and aspirin).

Statistical Analysis

We present the distribution of baseline characteristics of patients experiencing a first major, nuisance or clinically relevant nonmajor bleed during follow-up as medians for continuous variables (interquartile range: 25th–75th percentiles) and frequencies (percentages) for categorical variables. We present antithrombotic treatment patterns after the bleed and treatment patterns before the bleed descriptively with percentages and 95% confidence intervals.

We also evaluated event characteristics with respect to OAC discontinuation. Event characteristics of interest were abstracted from the medical records and included decrement in hemoglobin (fall in hemoglobin of ≥20 g L^{-1} [≥1.24 mmol L^{-1}]), blood transfusion (≥2 U of packed red blood cells or whole blood), and bleeding site (ear, nose, or throat; genitourinary; vascular access site; gastrointestinal; central nervous system [CNS]; perioperative; and other). Characteristics

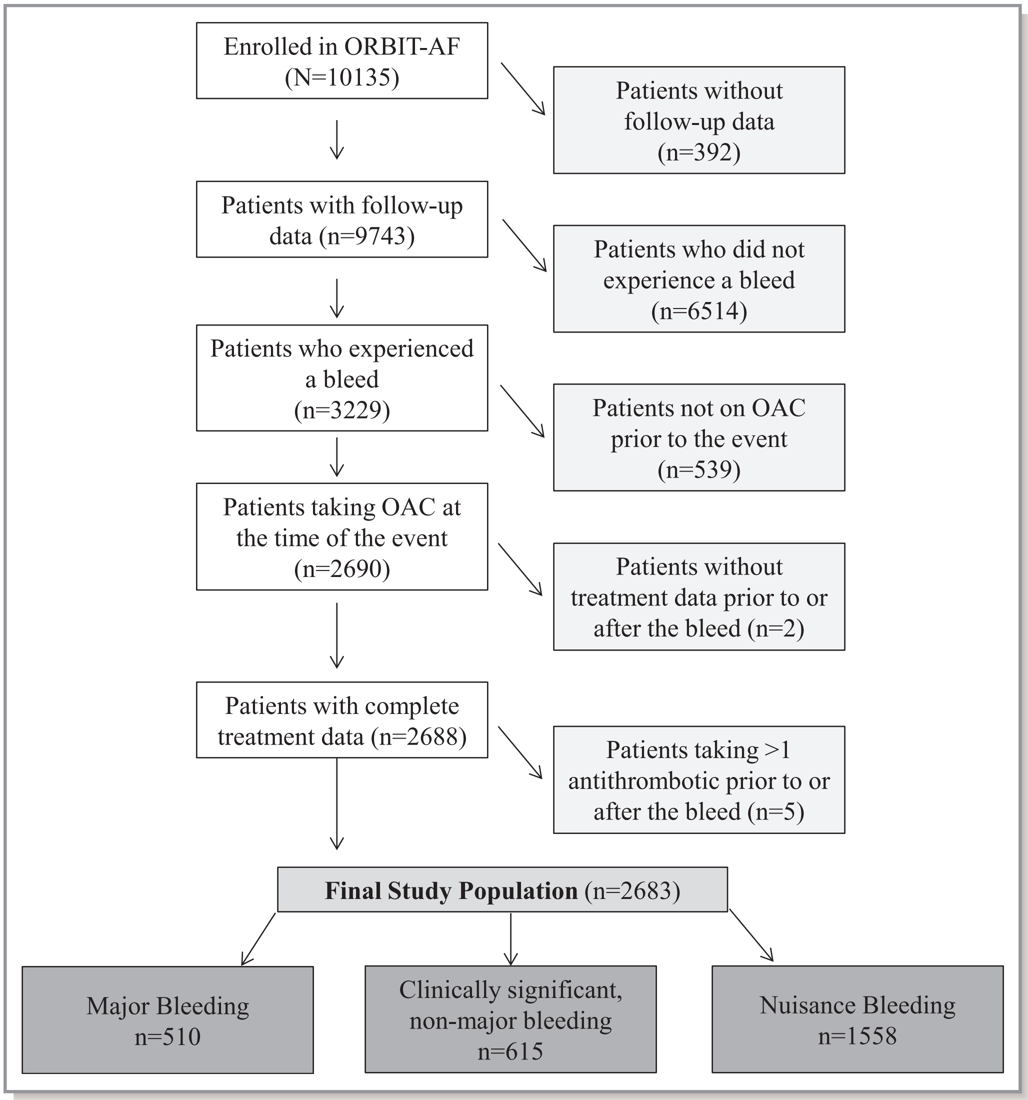

Figure. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for study exclusions. OAC indicates oral anticoagulation; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

of bleeds that were followed by OAC discontinuation were compared with those not followed by OAC discontinuation using χ^2 tests. We evaluated persistence on OAC by stroke risk using the CHA_2DS_2-VASc score, for which high stroke risk was defined as CHA_2DS_2-VASc $\geq$2 and low or medium stroke risk was defined as CHA_2DS_2-VASc <2 and history of gastrointestinal bleed. Finally, we evaluated multivariable associations between key patient characteristics and OAC discontinuation among patients experiencing bleeding events using a hierarchical logistic regression model with site included as a random effect and binary indicators for demographics and known risk factors. We included patients experiencing a nuisance, CRNM, or major bleed during the follow-up period. Covariate values were time-updated to values before the bleeding event. Single imputation was used to impute missing covariate values.

All *P* values presented are 2-sided, and $P<0.05$ was considered to be statistically significant for all analyses. Statistical analysis was performed using SAS software (v9.3; SAS Institute). All ORBIT-AF study participants gave written informed consent before enrollment. The Duke institutional review board approved ORBIT-AF, and all participating sites obtained approval from local institutional review boards before entering patient data.

Results

Baseline Characteristics

Among 9743 patients enrolled in ORBIT-AF with follow-up data, 510 (3.23/100 subject-years; 5.2%) experienced a major bleed, 615 (3.90/100 subject-years; 6.3%), experienced a clinically relevant nonmajor bleed, and 1558 (9.87/100 subject-years; 16.0%) experienced a nuisance bleed. Of 2683 patients who were taking anticoagulation therapy before experiencing a bleeding event, 90.1% were taking warfarin, 8.7% were taking dabigatran, 1.2% were taking rivaroxaban, and 0.04% were taking apixaban. Of 510 major bleeding events, 27 (5.3%) were fatal (0.15/100 subject-years). Compared with those who experienced a CRNM or nuisance bleed, patients who experienced a major bleed were on average more likely to be black and female (Table 1). Those experiencing major bleeds also had higher rates of heart failure, prior stroke, chronic kidney disease, anemia (before the bleed), and frailty than those experiencing a CRNM or nuisance bleed.

Table 2 displays major bleeding event characteristics by OAC persistence among nonfatal bleeds (n=483). The OAC discontinuation rate among patients who did not experience a bleed during follow-up was 17.2%. Compared with patients who persisted on OAC, those who discontinued were more likely to have a gastrointestinal or CNS bleed. With respect to acute bleeding management, there were no significant differences in decrement in hemoglobin or rate of transfusion by OAC persistence. Antithrombotic strategies following bleeding are shown by event type (major, CRNM, nuisance) and by pre-event antithrombotic medication in Table 3. More than half of patients who were taking OAC alone before a major bleeding event stayed on OAC alone following the bleed; however, nearly a quarter of patients discontinued all antithrombotic therapy following a major bleed. OAC discontinuation rates were highest following major bleeds (31.6%), followed by CRNM bleeds (12.7%) and nuisance bleeds (4.5%). Of 61 patients on OAC who switched to antiplatelet(s) at the time of the bleed, 18.0% switched to aspirin plus clopidogrel, 80.3% switched to aspirin only, and 1.6% switched to clopidogrel only.

Table 1. Baseline Characteristics of Major, CRNM, and Nuisance Bleeding

Variable	No Bleed (n=4772)	Major Bleed (n=510)	CRNM Bleed (n=615)	Nuisance (n=1558)
Age, y, median (IQR)	75.0 (66.0–81.0)	78.0 (71.0–82.0)	77.0 (70.0–83.0)	76.0 (69.0–82.0)
Female sex	41.3	48.0	43.3	44.4
Race				
White	88.3	91.4	91.4	92.0
Black or African American	5.5	4.9	2.3	2.8
Hispanic	4.5	2.4	5.2	3.6
Other	1.5	1.2	1.0	1.5
Medical history				
CHF	33.0	46.5	38.9	34.5
Prior stroke/TIA	15.7	20.0	15.9	17.5
COPD	13.9	24.5	22.0	19.3
Myocardial infarction	14.7	20.6	18.5	16.6
Current smoker	5.3	5.9	5.7	5.0
Diabetes mellitus	29.8	35.5	35.4	29.2
Hypertension	83.7	89.8	88.9	85.1
Obstructive sleep apnea	18.1	19.6	20.0	20.5
Chronic kidney disease	32.5	47.8	42.3	36.6
History of anemia	14.2	33.1	26.2	19.9
Frailty	4.8	8.4	5.2	5.8
Gastrointestinal bleed	7.0	12.9	10.1	8.6
Other intracranial bleed	0.6	0.8	0.8	0.7
BMI, kg/m^2	29.4 (25.6–34.5)	29.1 (25.1–33.7)	29.1 (25.6–33.6)	29.4 (25.6–34.1)
CHA_2DS_2-VASc, median (IQR)	4.0 (3.0–5.0)	5.0 (4.0–6.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
ORBIT-AF bleeding risk score, median (IQR)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)

BMI indicates body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant nonmajor; IQR, interquartile range; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; TIA, transient ischemic attack.

Table 2. Major Bleeding Event Characteristics by OAC Persistence (Nonfatal Events) in ORBIT-AF

	Persisted on OAC (N=330)	Discontinued OAC (N=153)	*P* Value*
Fall in hemoglobin†	69.1	68.6	0.9185
Transfusion‡	49.7	50.3	0.8976
Bleeding at a critical site	20.9	24.8	0.3341
Bleeding site			<0.0001
ENT	2.7	1.3	
Genitourinary	4.8	3.3	
Vascular access site	2.4	2.0	
Gastrointestinal	38.5	52.9	
CNS	5.2	15.7	
Perioperative	13.9	3.9	
Other	30.6	19.6	
Missing	1.8	1.3	

CNS indicates central nervous system; ENT, ear, nose, and throat; OAC, oral anticoagulation; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.
**P* values from χ^2 tests.
†Fall in hemoglobin of 20 g L^{-1} (1.24 mmol L^{-1}) or more.
‡≥2 U of packed red blood cells or whole blood.

Among patients experiencing a nuisance or CRNM bleed who were taking OAC alone before the event, the majority stayed on OAC only following the event. Less than 10% of CRNM bleeds and <3% of nuisance bleeds were discontinued from all antithrombotics. Patients taking novel OAC at the time of the major bleed were far more likely to switch to warfarin than warfarin patients were to switch to novel OAC (47.8% versus 4.9%, respectively). Table 4 displays results from the multivariable logistic regression model evaluating key patient characteristics and OAC discontinuation. We did not find significant associations between patient characteristics and discontinuation, with the exception of congestive heart failure, which was associated with an increased adjusted risk of OAC discontinuation after occurrence of a bleeding event (odds ratio: 1.32 [95% confidence interval, 1.02–1.72]; *P*=0.038).

In sensitivity analyses, we examined antithrombotic patterns following any bleeding event by stroke risk (CHA_2DS_2-VASc <2 versus ≥2) and by history of gastrointestinal bleed. OAC discontinuation rates were similar by stroke risk, with the majority of patients on dual therapy or OAC only persisting on their pre-event therapeutic regimens following the bleed (Table S1). Similar proportions of patients who were on dual therapy before the bleeding event remained on dual therapy after the bleeding event, for patients with and without a history of gastrointestinal bleed (Table S2). Among those taking OAC only before the bleeding event, a slightly higher proportion of patients without gastrointestinal bleeding history persisted on OAC only therapy following the event compared with patients who had a history of gastrointestinal bleeding (84.0% versus 78.9%, respectively). We also investigated the distribution of major bleeding event characteristics by age, race, and sex (Table S3). Although white patients were more likely to experience a fall in hemoglobin than nonwhite patients, and we observed some differences in bleeding site by age, the majority of event characteristics were similar by demographic subgroups.

Discussion

We examined acute management of bleeding and postbleeding antithrombotic strategies in a longitudinal prospective cohort of AF patients in a national US-based registry who were taking anticoagulant therapy before the bleeding event. Our major findings were as follows: First, persistence on OAC after a bleeding event was lowest for major bleeding, followed by CRNM and nuisance bleeding. Second, compared with patients who persisted on OAC following a major bleed, those who discontinued were more likely to have a gastrointestinal or CNS bleed and less likely to have a perioperative or ear, nose, or throat bleed. Third, nearly one third of patients who were on OAC before a major bleed were discontinued following the bleed (31.6%). Fourth, patterns of OAC therapy following any bleeding event were similar by CHA_2DS_2-VASc, but OAC discontinuation was higher for patients with a history of gastrointestinal bleeding (15.9%) compared with those without (10.8%).

Consistent with prior work, we found substantial rates of OAC discontinuation following major bleeding, despite increasing evidence that such discontinuations are associated with adverse clinical outcomes.[11] In a retrospective analysis of 442 patients experiencing warfarin-associated gastrointestinal bleeding, Witt et al reported warfarin discontinuation rates of 41.2% within 90 days of the index event. Patients who resumed warfarin within 90 days experienced substantially lower risks of thrombosis and all-cause mortality.[12] In another cohort study of AF patients experiencing a major gastrointestinal bleed in the Henry Ford Health System, Qureshi and colleagues reported warfarin discontinuation in 50.9% of patients. Those who restarted warfarin experienced no increased risk of recurrent gastrointestinal bleed and a substantially decreased risk of thromboembolism and death relative to those who discontinued therapy.[13] The slightly lower rates of OAC discontinuation observed in ORBIT-AF may be due to our inclusion of any major bleeding event meeting ISTH criteria, regardless of anatomical location. In our study, we observed an association between bleed location and OAC discontinuation, with gastrointestinal and CNS bleed more common among those who discontinued compared with those who persisted on OAC. However, even among gastrointestinal

Table 3. Antithrombotic Treatment Patterns Before and After Major, CRNM, and Nuisance Bleeding Events

Treatment After Bleed	Treatment Before Bleed: Overall	OAC+Antiplatelet(s)	OAC Only
Major bleeding events, n	483	226	257
OAC+antiplatelet(s)	27.3 (23.4–31.3)	47.4 (40.8–53.9)	9.7 (6.1–13.4)
OAC only	40.8 (36.4–45.2)	18.6 (13.5–23.7)	60.3 (54.3–66.3)
Antiplatelet(s) only	13 (10–16.1)	19.5 (14.3–24.6)	7.4 (4.2–10.6)
None	18.6 (15.2–22.1)	14.6 (10.0–19.2)	22.2 (17.1–27.3)
Missing	0.2	0.0	0.4
CRNM bleeding events, n	615	267	348
OAC+antiplatelet(s)	38.4 (34.5–42.2)	81.7 (77–86.3)	5.2 (2.9–7.5)
OAC only	48.9 (45.0–52.9)	7.1 (4–10.2)	81 (76.9–85.2)
Antiplatelet(s) only	7.2 (5.1–9.2)	9.4 (5.9–12.9)	5.5 (3.1–7.9)
None	5.5 (3.7–7.3)	1.9 (0.3–3.5)	8.3 (5.4–11.2)
Nuisance bleeding events, n	1558	570	988
OAC+antiplatelet(s)	34.8 (32.4–37.2)	86 (83.1–88.8)	5.3 (3.9–6.7)
OAC only	60.7 (58.3–63.1)	9.3 (6.9–11.7)	90.4 (88.6–92.2)
Antiplatelet(s) only	2.8 (2.0–3.6)	3.5 (2.0–5.0)	2.3 (1.4–3.3)
None	1.7 (1.0–2.3)	1.1 (0.2–1.9)	2 (1.2–2.9)
Missing	0.1	0.2	0.0

Data are shown as percentages and 95% confidence intervals. CRNM indicates clinically relevant nonmajor; OAC, oral anticoagulant.

bleeds, OAC discontinuation was lower than observed in prior work, possibly because of the longer period for assessment of warfarin resumption (up to 6 months) relative to the 60- and 90-day follow-up periods in the analyses by Qureshi et al and Witt et al, respectively.

Table 4. Associations Between Key Patient Characteristics and OAC Discontinuation Following Occurrence of a Bleeding Event* During Follow-up

Variable	OR (95% CI)	*P* Value	Global *P* Value
Congestive heart failure	1.32 (1.02–1.72)	0.0380	
Diabetes mellitus	1.25 (0.96–1.63)	0.0995	
Hypertension	1.29 (0.85–1.96)	0.2325	
Age 65–74 y (vs age <65 y)	1.11 (0.69–1.77)	0.6763	0.2892
Age ≥75 y (vs age <65 y)	1.33 (0.85–2.07)	0.2104	
Vascular disease	1.16 (0.89–1.51)	0.2736	
Black race (vs white)	1.75 (0.94–3.27)	0.0787	0.3151
Hispanic race (vs white)	1.11 (0.55–2.26)	0.7634	
Other race (vs white)	0.70 (0.20–2.39)	0.5644	
Female sex (vs male)	1.12 (0.86–1.44)	0.4017	
History of stroke/TIA	0.88 (0.63–1.22)	0.4314	

CI indicates confidence interval; OAC, oral anticoagulation; OR, odds ratio; TIA, transient ischemic attack.
*Based on the first bleeding event occurring during follow-up (nuisance, clinically relevant nonmajor, or major).

Although major bleeding events are an important factor in warfarin discontinuation,[14] few analyses have examined anticoagulation decisions following less severe events, which are far more common than major bleeding in AF. Prior work in a population of 2360 patients undergoing drug-eluting stent implantation suggests that nuisance bleeding may be important factor in long-term persistence,[15] with ≈11% of patients stopping clopidogrel use following nuisance bleeds. Our study builds on earlier work by examining antithrombotic strategies after major bleeding events in addition to milder bleeding events in AF. We observed less OAC discontinuation among patients experiencing nonmajor bleeding events than among major bleeding events, with 12.7% of patients discontinuing after a CRNM bleed and 4.5% discontinuing after a nuisance bleed. Although prior work suggests that milder bleeding is associated with decreased quality of life,[16] the relatively low rates of OAC discontinuation despite these events may reflect contemporary patient preferences regarding the balance of stroke prevention and avoidance of bleeding.[17] More work is needed to determine optimal education and shared decision-making strategies for patients at high risk of stroke who experience impairments in quality of life due to occurrence of nonmajor bleeding. Examination of real-world use of alternative stroke-prevention methods among patients who discontinued (eg, left atrial appendage occlusion, antithrombin antibodies) is also warranted.

Limitations

Our study has several limitations. First, the number of major bleeds occurring over follow-up was small, so our power to detect small differences in event characteristics by OAC discontinuation was limited. Second, because ORBIT-AF is a voluntary program, management patterns in this major bleeding population may not be representative of management patterns for other AF patients. Third, because CRNM and nuisance bleeding events and antithrombotic treatment status were captured at the same study visit, we were unable to identify exact dates and thus temporality of the bleeding event and OAC discontinuation. Fourth, we examined antithrombotic therapy at the visit following the major bleed; additional changes in OAC management following that visit may have occurred. Finally, our study addresses a knowledge gap regarding bleeding management in the era of novel OAC. More data are needed on the clinical impact of specific novel OAC reversal agents and bleeding management and decision algorithms among patients undergoing left atrial appendage occlusion and other alternative stroke-prevention therapies.

Conclusions

Overall, 1 in 3 patients who experienced a major bleed was no longer anticoagulated after a major bleeding event. Patients who discontinued OAC were more likely to have bleeding at a critical site than those who persisted on OAC. More research is needed to identify strategies to reduce patient-, provider-, and system-level barriers to optimal anticoagulation following a major bleed.

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Author Contributions

Dr O'Brien had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Antithrombotic strategies before and after a bleeding event by estimated stroke risk

CHA_2DS_2-VASc < 2					
		Overall N=97	**Treatment Prior to bleed**		
			TT N=2	**APT + OAC N=26**	**OAC Only N=69**
Treatment After Bleed	Triple therapy	---	---	---	---
	Antiplatelet +OAC	25.8	50.0	76.9	5.8
	OAC Only	64.9	0.0	11.5	87.0
	Dual Antiplatelet	2.1	50.0	3.8	0.0
	Antiplatelet Only	3.1	0.0	3.8	2.9
	No Antithrombotic Therapy	4.1	0.0	3.8	4.3
	Missing	---	---	---	---
CHA_2DS_2-VASc ≥ 2					
		Overall N=2559	**Treatment Prior to Bleed**		
			TT N=76	**APT + OAC N=959**	**OAC Only N=1524**
Treatment After Bleed	Triple therapy	2.0	42.1	1.1	0.5
	Antiplatelet +OAC	32.6	30.3	75.9	5.5
	OAC Only	54.0	7.9	10.9	83.3
	Dual Antiplatelet	1.0	11.8	0.5	0.7
	Antiplatelet Only	4.7	3.9	7.2	3.1
	No Antithrombotic Therapy	5.7	3.9	4.2	6.8
	Missing	0.1	0.0	0.1	0.1

APT = antiplatelet therapy; OAC = oral anticoagulation; TT = triple therapy.

Table S2. Antithrombotic strategies before and after a bleeding event by history of GI bleed.

No History of GI Bleed					
		Overall N=2397	**Treatment Prior to bleed**		
			TT N=71	**APT + OAC N=904**	**OAC Only N=1422**
Treatment After Bleed	Triple therapy	1.8	38.0	1.1	0.5
	Antiplatelet +OAC	33.0	31.0	76.1	5.6
	OAC Only	54.3	8.5	11.2	84.0
	Dual Antiplatelet	1.0	14.1	0.6	0.6
	Antiplatelet Only	4.5	4.2	7.1	3.0
	No Antithrombotic Therapy	5.3	4.2	3.9	6.2
	Missing	0.1	0.0	0.1	0.1
History of GI Bleed					
		Overall N=259	**Treatment Prior to Bleed**		
			TT N=7	**APT + OAC N=81**	**OAC Only N=171**
Treatment After Bleed	Triple therapy	2.3	71.4	1.2	0.0
	Antiplatelet +OAC	27.1	28.6	74.1	4.7
	OAC Only	54.8	0.0	8.6	78.9
	Dual Antiplatelet	1.2	0.0	1.2	1.2
	Antiplatelet Only	5.4	0.0	7.4	4.7
	No Antithrombotic Therapy	9.3	0.0	7.4	10.5
	Missing	---	---	---	---

APT = antiplatelet therapy; GI = gastrointestinal; OAC = oral anticoagulation; TT = triple therapy.

Table S3. Major bleeding event characteristics by age, race, and sex.

	Overall	Age<75 (n=187)	Age≥75 (n=296)	p-value‡	Male (n=249)	Female (n=234)	p-value‡	Non-White (n=39)	White (n=443)
Fall in hemoglobin*	68.9	71.1	67.6	0.4112	68.7	69.2	0.8951	51.3	70.4
Transfusion†	49.9	51.3	49.0	0.6152	47.0	53.0	0.1877	46.2	50.1
Bleeding in a critical site	22.2	21.9	22.3	0.9236	22.9	21.4	0.6872	25.6	21.9
Bleeding site				0.0019			0.4356		
ENT	2.3	2.7	2.0		2.8	1.7		0.0	2.5
GU	4.3	4.3	4.4		4.4	4.3		7.7	4.1
Vascular Access Site	2.3	4.3	1.0		2.0	2.6		5.1	2.0
GI	43.1	39.0	45.6		47.8	38.0		43.6	42.9
CNS	8.5	4.3	11.1		7.6	9.4		7.7	8.6
Perioperative	10.8	16.0	7.4		10.0	11.5		2.6	11.5
Other	27.1	27.3	27.0		24.1	30.3		30.8	26.9
Missing	1.7	2.1	1.4		1.2	2.1		2.6	1.6

CNS = central nervous system; ENT = ear, nose and throat; GI = gastrointestinal; GU = genitourinary.
*Fall in hemoglobin of 20 g L^{-1} (1.24 mmol L^{-1}) or more
†2 or more units of packed red blood cells or whole blood
‡p-values from chi-squared tests