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

Permalink
https://escholarship.org/uc/item/6gg096nx

Journal
Journal of the American Heart Association, 7(12)

ISSN
2047-9980

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

Publication Date
2018-06-09

DOI
10.1161/jaha.117.006391

Peer reviewed
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). 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. 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. However, the decision to discontinue or modify
Therapeutic Strategies Following Bleeding in AF

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.

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. 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. 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
of bleeds that were followed by OAC discontinuation were compared with those not followed by OAC discontinuation using $\chi^2$ tests. We evaluated persistence on OAC by stroke risk using the CHA$_2$DS$_2$-VASc score, for which high stroke risk was defined as CHA$_2$DS$_2$-VASc $\geq$ 2 and low or medium stroke risk was defined as CHA$_2$DS$_2$-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/m²                                      | 29.4 (25.6–34.5)  | 29.1 (25.1–33.7)    | 29.1 (25.6–33.6)    | 29.4 (25.6–34.1)  |
| CHA2DS2-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.
Therapeutic Strategies Following Bleeding in AF

O’Brien et al

DOI: 10.1161/JAHA.117.006391
Journal of the American Heart Association

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

| Bleeding Event Characteristics | 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 χ² 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 (CHA²DS²-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 CHA²DS²-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. 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. 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. 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
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.

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

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.

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).
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.

Acknowledgments

The authors would like to thank ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) staff and participants for their important contributions to this work.

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.

Sources of Funding

ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ.

Disclosures

Dr O’Brien reports research grants from Janssen, BMS, Novartis (significant); Sanofi (modest). Dr Fonarow reports consulting for Janssen (significant). Dr Kowey reports consulting for Johnson & Johnson (significant). Dr Ansell reports consulting/advisory board for Bristol-Myers Squibb, Pfizer, Janssen, Boehringer Ingelheim, and Daiichi Sankyo; equity interest in PertoPher. Dr Mahaffey reports research support from AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Portola, POZEN, Schering-Plough, and The Medicines Company, and consulting agreements with Amgen, AstraZeneca, Glaxo SmithKline, Johnson & Johnson, and Merck. Dr Gersh reports consultancies with Janssen Scientific Affairs (significant) and Cipla Limited Data Safety Monitoring Board (modest) for Mount Sinai St. Lukes, Boston Scientific Corporation, Teva Pharmaceutical Industries, St. Jude Medical, Janssen Research & Development, Baxter Healthcare Corporation, Thrombosis Research Institute, Duke Clinical Research Institute, Duke University, Kowa Research Institute, and Cardiovascular Research Foundation. Dr Peterson reports significant research support from Eli Lilly & Company, Daiichi Sankyo and Janssen. Dr Piccini reports significant research support from Boston Scientific, ResMed, ARCA Biopharma, St. Jude Medical Center, Gilead Sciences, Johnson&Johnson, Spectranetics, and Janssen and consultancies to Janssen (significant), Spectranetics (significant), Medtronic (significant), Forest Laboratories (modest), Pfizer (Modest), and Glaxo SmithKline (modest). Dr Hylek reports consultant/advisory board for Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Johnson & Johnson, Pfizer. Research grants from: Bristol-Myers Squibb, Ortho-McNeil-Janssen. Speaker fees for: Boehringer Ingelheim; Bristol-Myers Squibb.

References

1. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 1991;84:527–539.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–867.
3. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen K, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterpey A, Tamargo JL, Zamarro JL, ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114:e257–e354. Erratum in: Circulation. 2007;116:e138.
4. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: Analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449–1457.

DOI: 10.1161/JAHA.117.006391
5. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet*. 1996;348:633–638.

6. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ*. 2013;185:E121–E127.

7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.

8. Siegal DM, Crowther MA. Acute management of bleeding in patients on novel oral anticoagulants. *Eur Heart J*. 2013;34:489–498b.

9. Piccini JP, Fraulo ES, Ansell JE, Fonarow GC, Gersh BJ, Go AS, Hylek EM, Kowey PR, Mahaffey KW, Thomas LE, Kong MH, Lopes RD, Mills RM, Peterson ED. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J*. 2011;162:606–612.e1.

10. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.

11. Staerk L, Lip GY, Olesen JB, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TS, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2015;351:h5876.

12. Witt DM, Delate T, Garcia DA, Clark NP, Hylek EM, Ageno W, Dentali F, Crowther MA. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med*. 2012;172:1484–1491.

13. Qureshi W, Mittal C, Patias I, Garikapati K, Kuchipudi A, Cheema G, Elbatta M, Alirhayim Z, Khalid F. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol*. 2014;113:662–668.

14. O’Brien EC, Simon DN, Allen LA, Singer DE, Fonarow GC, Kowey PR, Thomas LE, Ezekowitz MD, Mahaffey KW, Chang P, Piccini JP, Peterson ED. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am J Cardiol*. 2014;168:487–494.

15. Roy P, Bonello L, Torguson R, de Labriolle A, Lemesle G, Slottow TL, Steinberg DH, Kaneshige K, Xue Z, Satler LF, Kent KM, Sudath WO, Pichard AO, Lindsay J, Waksman R. Impact of “nuisance” bleeding on clopidogrel compliance in patients undergoing intracoronary drug-eluting stent implantation. *Am J Cardiol*. 2008;102:1614–1617.

16. Amin AP, Buchuwar A, Reid KJ, Chhariwalla AK, Salisbury AC, Yeh RW, Kosiborod M, Wang TY, Alexander KP, Gosch K, Cohen DJ, Spertus JA, Bach RG. Nuisance bleeding with prolonged dual antiplatelet therapy after acute myocardial infarction and its impact on health status. *J Am Coll Cardiol*. 2013;61:2130–2138.

17. Lahaye S, Regpala S, Lacombe S, Sharma M, Gibbens S, Bail D, Francis K. Evaluation of patients’ attitudes towards stroke prevention and bleeding risk in atrial fibrillation. *Thromb Haemost*. 2014;111:465–473.

DOI: 10.1161/JAHA.117.006391
SUPPLEMENTAL MATERIAL
Table S1. Antithrombotic strategies before and after a bleeding event by estimated stroke risk

| Treatment After Bleed | Overall N=97 | Treatment Prior to bleed | APT + TT N=2 | OAC N=26 | OAC Only N=69 |
|-----------------------|--------------|--------------------------|-------------|----------|--------------|
| Triple therapy        | 25.8         | 50.0                     | 76.9        | 5.8      |
| Antiplatelet + OAC    | 64.9         | 0.0                      | 11.5        | 87.0     |
| OAC Only              | 2.1          | 50.0                     | 3.8         | 0.0      |
| Dual Antiplatelet     | 3.1          | 0.0                      | 3.8         | 2.9      |
| Antiplatelet Only     |              |                          |             |          |
| No Antithrombotic Therapy | 4.1      | 0.0                      | 3.8         | 4.3      |
| Missing               |              |                          |             |          |

| Treatment After Bleed | Overall N=2559 | Treatment Prior to Bleed | APT + TT N=76 | OAC N=959 | OAC Only N=1524 |
|-----------------------|-----------------|--------------------------|---------------|-----------|-----------------|
| 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 | Treatment Prior to bleed | Overall | N=2397 | Treatment After Bleed | N=71 | APT + OAC | N=904 | OAC Only | N=1422 |
|------------------------|--------------------------|---------|--------|-----------------------|------|----------|--------|----------|--------|
|                        |                          | Triple therapy | 1.8 | TT | 38.0 | 1.1 | 0.5 | 4.1 |
|                        |                          | Antiplatelet + OAC | 33.0 | APT + OAC | 31.0 | 76.1 | 5.6 | 4.1 |
|                        |                          | OAC Only | 54.3 | OAC Only | 8.5 | 11.2 | 84.0 | 4.1 |
|                        |                          | Dual Antiplatelet | 1.0 | Dual Antiplatelet | 14.1 | 0.6 | 0.6 | 4.1 |
|                        |                          | Antiplatelet Only | 4.5 | Antiplatelet Only | 4.2 | 7.1 | 3.0 | 4.1 |
|                        |                          | No Antithrombotic Therapy | 5.3 | No Antithrombotic Therapy | 4.2 | 3.9 | 6.2 | 4.1 |
|                        |                          | Missing | 0.1 | Missing | 0.0 | 0.1 | 0.1 | 4.1 |

| History of GI Bleed | Treatment Prior to Bleed | Overall | N=259 | Treatment After Bleed | TT | APT + OAC | OAC Only | OAC Only |
|---------------------|--------------------------|---------|--------|-----------------------|-----|----------|----------|----------|
|                     |                          | Triple therapy | 2.3 | TT | 71.4 | 1.2 | 0.0 | 4.1 |
|                     |                          | Antiplatelet + OAC | 27.1 | APT + OAC | 28.6 | 74.1 | 4.7 | 4.1 |
|                     |                          | OAC Only | 54.8 | OAC Only | 0.0 | 8.6 | 78.9 | 4.1 |
|                     |                          | Dual Antiplatelet | 1.2 | Dual Antiplatelet | 0.0 | 1.2 | 4.1 | 4.1 |
|                     |                          | Antiplatelet Only | 5.4 | Antiplatelet Only | 0.0 | 7.4 | 4.7 | 4.1 |
|                     |                          | No Antithrombotic Therapy | 9.3 | No Antithrombotic Therapy | 0.0 | 7.4 | 10.5 | 4.1 |
|                     |                          | Missing | --- | Missing | --- | --- | --- | --- |

APT = antiplatelet therapy; GI = gastrointestinal; OAC = oral anticoagulation; TT = triple therapy.
Table S3. Major bleeding event characteristics by age, race, and sex.

|                       | Overall (n=187) | Age<75 (n=296) | Age≥75 (n=296) | 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         |                |                |                |              |               |          |                  |               |
| 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