

Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: Findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry

Emily C. O'Brien, PhD,^a DaJuanicia N. Holmes, MS,^a Jack E. Ansell, MD,^b Larry A. Allen, MD, MHS,^c Elaine Hylek, MD,^d Peter R. Kowey, MD,^e Bernard J. Gersh, MB, ChB, DPhil,^f Gregg C. Fonarow, MD,^g Christopher R. Koller, BA,^a Michael D. Ezekowitz, MB, ChB, DPhil,^c Kenneth W. Mahaffey, MD,^h Paul Chang, MD,ⁱ Eric D. Peterson, MD, MPH,^a Jonathan P. Piccini, MD, MHS,^a and Daniel E. Singer, MD, MA^j *Durham, NC; New York, NY; Aurora, CO; Boston, MA; Philadelphia, PA; Rochester, MN; Los Angeles, and Stanford, CA; and Raritan, NJ*

Background Oral anticoagulation (OAC) therapy reduces the risk of thromboembolic events associated with atrial fibrillation (AF), yet a substantial proportion of patients with AF are not prescribed OAC. The aim of this study is to describe the frequencies of and factors associated with OAC contraindications in contemporary clinical practice.

Methods We analyzed data from the ORBIT-AF study, a national, prospective, outpatient registry of incident and prevalent AF. Oral anticoagulation contraindications were uniformly collected at enrollment by site personnel using a predefined list. Baseline patient and provider characteristics were compared between participants with and without documented OAC contraindications.

Results From June 2010 to August 2011, 10,130 patients 18 years or older with electrocardiographically documented AF were enrolled at 176 practices. Of these, 1,330 (13.1%) had contraindications documented at the baseline visit: prior bleed (27.7%), patient refusal/preference (27.5%), high bleeding risk (18.0%), frequent falls/frailty (17.6%), need for dual antiplatelet therapy (10.4%), unable to adhere/monitor warfarin (6.0%), comorbid illness (5.3%), prior intracranial hemorrhage (5.0%), allergy (2.4%), occupational risk (0.8%), pregnancy (0.2%), and other (12.6%). Among patients with reported contraindications, 30.3% were taking warfarin or dabigatran, as compared with 83.0% of those without reported contraindications. Besides "patient refusal/preference," being labeled as having frequent falls or being frail was associated with the lowest OAC use among patients with high stroke risk.

Conclusions Contraindications to OAC therapy among patients with AF are common but subjective. Many patients with reported contraindications were receiving OAC, suggesting that the perceived benefit outweighed the potential harm posed by the relative contraindication. (*Am Heart J* 2014;167:601-609.e1.)

From the ^aDuke Clinical Research Institute, Durham, NC, ^bNew York University School of Medicine, Lenox Hill Hospital, New York, NY, ^cUniversity of Colorado School of Medicine, Aurora, CO, ^dBoston University School of Medicine, Boston, MA, ^eJefferson Medical College, Philadelphia, PA, ^fMayo Clinic, Rochester, MN, ^gUCLA Division of Cardiology, Los Angeles, CA, ^hStanford University School of Medicine, Stanford, CA, ⁱJanssen Scientific Affairs, Raritan, NJ, and ^jHarvard Medical School and Massachusetts General Hospital, Boston, MA.

William G. Stevenson, MD, served as guest editor for this article.

Submitted October 17, 2013; accepted December 21, 2013.

Reprint requests: Emily O'Brien, PhD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27705.

E-mail: emily.obrien@duke.edu

0002-8703/\$ - see front matter

© 2014, Mosby, Inc. All rights reserved.

<http://dx.doi.org/10.1016/j.ahj.2013.12.014>

Oral anticoagulants (OACs) reduce the risk of thromboembolic events associated with atrial fibrillation (AF),^{1,2} yet recent evidence suggests that many high-risk patients with AF are not taking OAC.³ Underuse of OAC is often attributed to treatment contraindications that create an unfavorable risk/benefit profile for OAC therapy. Evidence suggests that old age, language abilities, race, and patient-related and provider-related reasons may determine which patients receive OAC,^{4,5} yet little is known about the major factors associated with documented OAC contraindications in contemporary practice. Furthermore, perceived OAC contraindications are highly variable and often differ from one provider to another. Recent evidence suggests that anticoagulation treatment decisions are more likely to be driven by perceived risks (such as adverse bleeding

events) than by perceived benefits (such as stroke risk reduction),^{6,7} but the extent to which this is reflected in the specific contraindications documented by the provider is unknown.

In this study, we aimed to describe patterns of documented contraindications to OAC therapy measured at baseline in a large, contemporary outpatient AF cohort. We also aimed to assess associations between clinical and demographic factors and overall OAC contraindications, according to whether contraindications were related to an active or past clinical condition ("event related") or were related to patient preference or perceived inability to adhere to the prescribed medication and monitoring regimen ("patient-related").

Methods

Study population

We used data from the ORBIT-AF study. The study design and population of ORBIT-AF have been described in detail.⁸ Briefly, ORBIT-AF is a national, prospective registry to improve the quality of care and outcomes for patients with AF. Eligible patients 18 years and older who were able to provide informed consent and follow-up information were consecutively enrolled at 176 sites nationwide. Participating sites were selected to be geographically representative and to include a diverse set of providers who manage patients with AF, including cardiologists, electrophysiologists, and primary care providers. Study design and management were conducted by the Duke Clinical Research Institute. Using information from the medical record, sites entered data on demographics, clinical comorbidities, AF treatment strategy, and provider characteristics into an interactive, Web-based data collection form. Longitudinal information was collected at 6-month intervals for 2 years after initial enrollment and included information on vital status, hospitalizations, bleeding events, pharmacotherapy, procedures, and quality of life.

From June 2010 to August 2011, 10,132 patients were enrolled in ORBIT-AF. We excluded 2 patients with missing information on OAC contraindications, for a final study population of N = 10,130 from 176 sites.

OAC contraindication

The primary study outcome was any documented contraindication to OAC therapy documented by the provider at the baseline enrollment visit and documented in the medical record. For all patients with a contraindication to OAC, providers were asked to select 1 or more specified contraindications from a predefined list. The following contraindications were collected: allergy to OAC, comorbid illness, prior intracranial hemorrhage, pregnancy, prior bleed, patient refusal/preference, inability to adhere to/monitor therapy, high bleeding risk, need for dual antiplatelet therapy, occupational risk, frequent falls/frailty, and other. Respondents could select more than 1 contraindication from the predefined list. The set of specific OAC contraindications was selected and approved based on clinical relevance by the ORBIT-AF executive committee during the study design phase. We assessed the association of contraindications with objective bleed risk using the ATRIA bleeding score⁹ and objective AF stroke risk using the CHADS₂¹⁰ and CHA₂DS₂-VASc¹¹ scores.

Event-related and patient-related contraindications

We conducted a set of secondary analyses to determine the association between baseline characteristics and 2 contraindication subtypes: event-related contraindications and patient-related contraindications. Event-related contraindications included the following: prior intracranial hemorrhage, prior bleed, allergy, comorbid illness, and pregnancy. Patient-related contraindications were identified for patients who listed any non-event-related contraindication (patient refusal/preference, inability to adhere to/monitor therapy, high bleeding risk, need for dual antiplatelet therapy, occupational risk, frequent falls/frailty, and other). Patients with both an event-related and a patient-related contraindication listed were classified as both.

Statistical analysis

We compared specific OAC contraindication category rates by age, bleeding risk, and stroke risk using Pearson χ^2 tests for categorical variables. Next, we compared the distribution of baseline characteristics between patients with a documented contraindication to OAC therapy and those without using Pearson χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. We also compared OAC treatment rates within each contraindication category and by CHADS₂ score using Pearson χ^2 tests. To determine factors associated with OAC contraindication, we constructed multivariable logistic regression models with the binary outcome of any contraindication documented at baseline vs none. All models were fit using generalized estimating equations (GEEs) with exchangeable working correlation matrix to account for within-site clustering.¹²

Candidate variables for modeling were selected using clinical knowledge and included demographics, relevant comorbidities, AF diagnosis type, management strategy, past procedures and interventions, laboratory data, and vital signs. The full list of candidate variables for modeling is provided in [online Appendix](#). Continuous variables were evaluated for nonlinearity with the outcome, and nonlinear relationships were addressed by using linear splines. Missing data were multiply-imputed, and final estimates and SEs reflect the combined analysis for 5 imputed data sets. Final estimates are presented as odds ratios with corresponding 95% CIs. Rates of missing data were less than 2% for all candidate variables in the model, with the following exceptions: level of education (4.3%) and hematocrit (11%). We used backward selection with a stay criterion of 0.05 on the first imputed data set to obtain a set of factors in which each factor was independently associated with a documented baseline contraindication. We repeated this strategy for the secondary binary outcomes of event-related contraindication (vs no event-related contraindication) and patient-related contraindication (vs no patient-related contraindication).

All statistical analyses for this study were performed using SAS software (version 9.3; Cary, NC). All *P* values presented are 2 sided. All ORBIT-AF participants provided written informed consent prior to study participation. The Duke Institutional Review Board approved the ORBIT-AF Registry, and participating sites obtained approval from local institutional review boards prior to entering patient data.

Table I. Documented OAC contraindications* (percent) overall and by patient age, bleeding, and stroke risk

Contraindication†	Overall (n = 1330)	Age (y)			ATRIA bleeding score			CHADS ₂			CHA ₂ DS ₂ -VASc		
		<75 (n = 493)	≥75 (n = 837)	P§	<5 (n = 929)	≥5 (n = 400)	P§	<2 (n = 312)	≥2 (n = 1018)	P§	<2 (n = 81)	≥2 (n = 1249)	P§
Prior bleed	27.7	21.1	31.7	<.0001	21.6	42.0	<.0001	16.7	31.1	<.0001	13.6	28.7	.003
Patient refusal	27.5	31.6	25.1	.01	30.6	20.5	.0002	42	23.1	<.0001	48.2	26.2	<.0001
High bleeding risk	18.0	15.4	19.5	.06	13.7	27.8	<.0001	10.3	20.3	<.0001	6.2	18.7	.004
Frequent falls/frailty	17.6	5.9	24.5	<.0001	14.8	24.0	<.0001	7.4	20.7	<.0001	2.5	18.6	.0002
Need for dual APT	10.4	12.0	9.4	.14	12.3	6.0	.001	10.9	10.2	.73	4.9	10.7	.10
Unable to adhere	6.0	7.3	5.3	.13	6.9	4.0	.04	5.1	6.3	.45	6.2	6.0	.95
Comorbid illness	5.3	6.1	4.8	.30	3.4	9.5	<.0001	3.2	5.9	.06	2.5	5.4	.24
Prior intracranial hemorrhage	5.0	5.1	4.9	.89	5.1	4.8	.81	3.2	5.5	.10	3.7	5.0	.59
Allergy	2.4	3.9	1.6	.01	3.0	1.0	.03	3.5	2.1	.14	3.7	2.3	.43
Occupational risk	0.8	1.4	0.5	.07	1.1	0.3	.13	1.9	0.5	.01	2.4	0.7	.09
Pregnancy	0.2	0.4	0.1	.29	0.2	0.3	.90	0.3	0.2	.69	0.0	0.2	.66
Other	12.6	15.8	10.6	.01	14.5	7.8	.001	18	10.9	.001	24.7	11.8	.001

* Among patients who listed a contraindication.
† Respondents could select more than 1 contraindication.
§ Pearson χ^2 tests.

Results

Of the 10,130 patients enrolled in ORBIT-AF, 1,330 (13.1%) had contraindications to OAC. Table I shows the distribution of specific OAC contraindications among ORBIT-AF patients who listed a contraindication. Overall, the most commonly reported contraindications were patient refusal and prior bleed, both of which were listed for more than one-quarter of contraindicated patients. Other commonly listed contraindications were high bleeding risk (18.0%), frequent falls/frailty (17.6%), other (12.6%), and need for dual antiplatelet therapy (10.4%). Patients 75 years and older were more likely have prior bleed, frequent falls/frailty, and high bleeding risk documented as reasons for nontreatment compared with younger patients, who were more likely to list contraindications related to patient refusal. Of note, physician-reported contraindications of “high bleeding risk” and “frequent falls/frailty” were associated with higher objective bleeding risk (ATRIA bleeding score).

Given that assessment of OAC contraindication is most relevant in patients with indication for treatment, we examined the distribution of contraindications stratified by CHADS₂ score. A small percentage of the population with contraindications had a CHADS₂ score of 0 (6.5%); therefore, we combined these patients and those with a CHADS₂ score of 1 into a single category. Compared with patients without contraindications, those with documented contraindications had a higher mean CHADS₂ score (2.5 vs 2.2) (Table II) and were more likely to be classified as high stroke risk (CHADS₂ ≥ 2; 76.5% vs 70.5%). The distribution of specific contraindications differed by estimated stroke risk (Table I). Among patients with low stroke risk (CHADS₂ < 2) and with contraindications, the most common contraindication was patient refusal (42%), nearly twice the frequency as in patients with high

stroke risk (CHADS₂ ≥ 2). Compared with patients with low stroke risk, patients with high stroke risk were more likely to list prior bleed (31.1% vs 16.7%), high bleeding risk (20.3% vs 10.3%), and frequent falls/frailty (20.7% vs 7.4%) as OAC contraindications.

The distribution of baseline characteristics by documented contraindications is shown in Table II. Patients with an OAC contraindication were older on average than patients without a documented contraindication. Patients with contraindications were more likely to have congestive heart failure, chronic kidney disease, history of stroke, history of myocardial infarction (MI), and peripheral vascular disease than noncontraindicated patients. Similarly, patients with contraindications had both higher objective bleed (ATRIA) and stroke risk (CHADS₂ and CHA₂DS₂-VASc) scores.

Only 30% of patients with a documented contraindication were taking OAC compared with 83% of those without a documented contraindication ($P < .0001$) (Table II). Among patients with documented contraindications who were still taking OAC, the most commonly listed contraindications were prior bleed (25.8%), need for dual antiplatelet therapy (24.3%), and high bleeding risk (15.4%) (Table III).

Correlates of contraindications

Prior cardioversion, higher hematocrit, higher education, higher body mass index and higher glomerular filtration rate (GFR) were all independently associated with decreased odds of a documented contraindication of any type. Factors independently associated with increased odds of any OAC contraindication included age ≥ 75 years, smoking history, prior stroke, prior MI, cognitive impairment/dementia, sinus rhythm, and prior AV node ablation (Figure 1).

Table II. Baseline characteristics of patients with AF by OAC contraindications documented at baseline

Variable*	Patients without contraindications (n = 8800; 86.9%)	Patients with contraindications (n = 1330; 13.1%)	P†
Age (y), median (IQR)	74.0 (66.0-81.0)	79.0 (70.0-85.0)	<.0001
Male gender	58.0	55.5	.0855
Black race	4.9	5.7	.4112
Comorbidities			
Heart failure	31.9	36.6	.0006
Prior stroke	8.4	12.1	<.0001
Prior MI	15.2	20.2	<.0001
Chronic kidney disease	33.1	41.1	<.0001
Peripheral vascular disease	12.6	18.4	<.0001
Smoking history	47.7	52.3	.0018
Frailty	4.5	14.2	<.0001
Obstructive sleep apnea	18.4	16.8	.1535
CHADS ₂ , mean (SD)	2.2 (1.3)	2.5 (1.4)	<.0001
CHA ₂ DS ₂ -VASc, mean (SD)	3.8 (1.8)	4.3 (1.8)	<.0001
ATRIA bleeding score, mean (SD)	2.7 (1.9)	3.5 (2.2)	<.0001
AF diagnosis			
First detected/new onset	4.9	3.7	.006
Paroxysmal	50.2	52.7	
Persistent	17.2	14.2	
Permanent	27.7	29.4	
Geographic region			
Midwest	26.3	21.4	.0007
Northeast	25.3	27.4	
South	34.4	35.1	
West	14.0	16.1	
Education			
Some high school	13.3	18.7	.0001
High school	51.3	49.3	
College	22.7	21.2	
Postgraduate	8.3	7.4	
Provider specialty			
Cardiology	79.7	82.3	.0236
Internal medicine/primary care	67.5	65.4	.1381
Electrophysiology	17.2	14.8	.0277
Neurology	2.2	1.7	.2121
Currently taking OAC‡	83.0	30.3	<.0001

Abbreviation: IQR, Interquartile range.

*All data presented as percentages unless otherwise indicated.

†P values from Pearson χ^2 for categorical variables and Wilcoxon rank sum for continuous variables.

‡Warfarin or dabigatran.

Overall, 78.5% of contraindications listed were patient related, compared with 37.1% that were event related. Patients with high stroke risk reported event-related contraindications (41.4%) more commonly than patients with low stroke risk (23.4%). Patients 75 years and older had a similar rate of patient-related contraindications (78.3%) as younger patients (78.9%) but a higher rate of event-related contraindications (39.7% vs 32.9%).

Results from the multivariable analyses of event-related contraindications are shown in Figure 2. For models of baseline characteristics and patient-related contraindications, associations were similar for all variables in magnitude and direction to those from the model of any contraindication, except for prior stroke, prior MI, and estimated GFR, which were no longer significant (data not shown). Event-related contraindications were inversely associated with higher hematocrit, prior car-

dioversion, and higher GFR. Presence of an implanted device, male gender, prior MI, chronic obstructive pulmonary disease, older age, and prior stroke were all positively associated with event-related contraindication.

OAC treatment by specific contraindication

To assess the relative nature of documented OAC contraindications in clinical practice, we examined treatment rates within each specific contraindication category (Figure 3). To promote stability in estimates, we included only categories with at least 15 patients with that specific contraindication documented. The lowest OAC treatment rates were observed among patients with contraindications due to patient refusal or preference, frequent falls/frailty, and other, whereas the highest rates were observed among patients with contraindications due to comorbid illness, inability to adhere/monitor

Table III. Patients with a documented contraindication* who were still treated with OAC†: distribution of contraindications

Contraindication‡	% (n = 403)
Prior bleed	25.8
Need for dual antiplatelet therapy	24.3
High bleeding risk	15.4
Frequent falls/frailty	14.4
Patient refusal/preference	12.4
Comorbid illness	8.2
Unable to adhere/monitor	6.2
Prior intracranial hemorrhage	4.5
Allergy	2.0
Occupational risk	1.5
Pregnancy	0.5
Other	8.4

* Among patients who listed a contraindication.

† Warfarin or dabigatran.

‡ Respondents could select more than 1 contraindication.

warfarin, and need for dual antiplatelet therapy. When examining treatment within each contraindication stratum by CHADS₂ score (<2 and ≥2) (Figure 4), we found higher treatment rates among patients with high stroke risk for most contraindication categories. However, we observed similar or higher OAC treatment rates among patients with low stroke risk for patients with contraindications due to prior bleed, high bleeding risk, inability to adhere/monitor warfarin, and need for dual antiplatelet therapy. Among patients with high stroke risk (CHADS₂ score ≥2), particularly low use of OAC was seen in those labeled as having frequent falls or frail.

Discussion

Proper use of anticoagulation is vital to reducing stroke risk among patients with AF, yet OAC is substantially underused in clinical practice.^{4,13,14} We examined patterns of OAC contraindication and associated baseline factors in a large contemporary outpatient population of AF. Our major findings are as follows: (1) 13.1% of patients in our study population had a documented contraindication to OAC at baseline; (2) patients with perceived contraindications were, on average, older, sicker, and more often frail, but also at higher stroke risk; (3) the most common specific contraindications were patient refusal, prior bleed, frequent falls/frailty, and high bleeding risk; (4) patients with low stroke risk were more likely to report patient refusal as the reason for nontreatment, whereas higher-risk patients more often reported reasons related to frequent falls and history of bleeding; (5) of patients with AF and with a contraindication to OAC, 30% were still taking OAC at the baseline study visit; and (6) having frequent falls or being labeled as frail was associated with a notably low frequency of OAC use among patients at high risk for stroke.

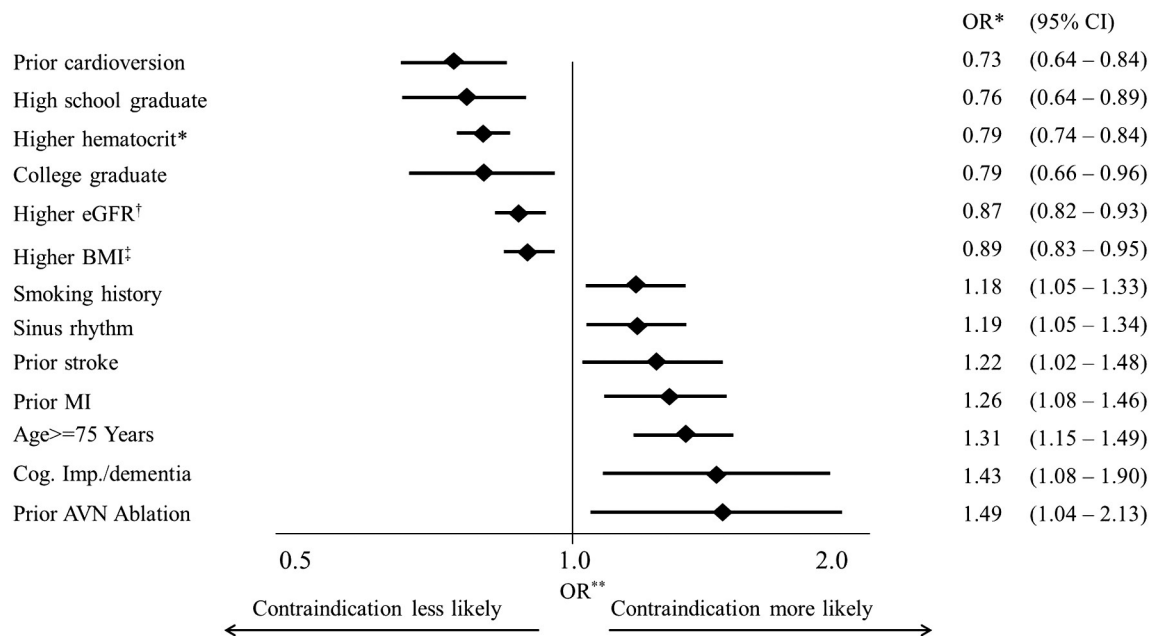
Current estimates of OAC contraindication are highly dependent on the selected definition of “contraindica-

tion” and, as a result, vary widely across studies. Results from our study are similar to those from electrocardiogram-confirmed patients with AF seen in general medicine clinics in the United Kingdom, which documented a “major contraindication” rate of 13%.¹⁵ In a retrospective review of patients with AF managed by primary care providers, contraindications were reported for 18% of patients when classifying contraindications according to warfarin treatment guidelines in the package insert.¹⁶ Similar estimates have been reported from other analyses using comparable definitions of OAC contraindications.¹⁷ Conversely, other studies have estimated OAC contraindication rates as high as 50% to 66%.^{18,19} The Cardiovascular Health Study reported a “potential contraindication” rate of 58% when using an expanded set of contraindications that included consumption of more than 28 alcoholic drinks per week, a score in the lowest 5% of cognitive function measures, or a history of falls.²⁰ Our study expands on existing work by characterizing specific contraindications to OAC in a large, US-based AF cohort. In addition to assessing overall contraindication patterns, we incorporated comprehensive clinical information to assess the influence of stroke risk on OAC treatment among contraindicated patients, an integral element to OAC treatment decisions that has been infrequently considered in prior analyses. Furthermore, because information on contraindications was collected for all patients, we were able to examine OAC contraindication patterns independent of treatment status, an advantage compared with analyses that collect contraindication information only among untreated patients.

We found associations between a number of baseline characteristics and OAC contraindications in multivariable regression models. Higher hematocrit and estimated GFR were associated with a decreased likelihood of OAC contraindication, whereas older age, prior stroke, prior MI, and cognitive impairment/dementia were associated with increased odds of OAC contraindication. These results indicate that a patient's comorbidity burden independently contributes to the likelihood of receiving OAC, even after accounting for patient age. These associations were in the same direction and even greater in magnitude for models of event-related contraindications.

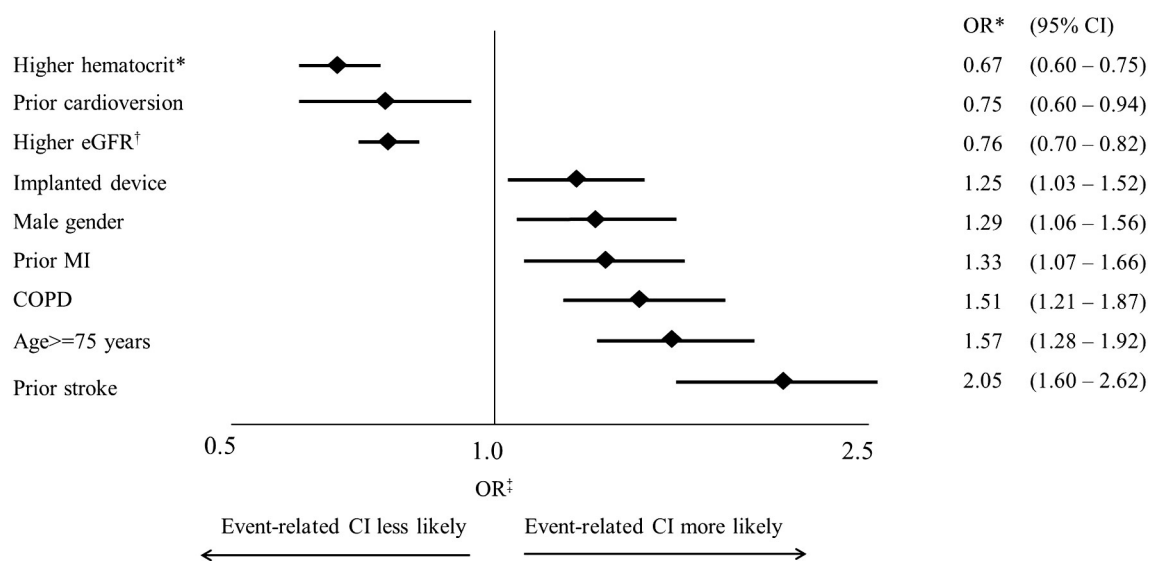
There is currently a lack of consensus on which OAC contraindications should be considered “absolute” and which should be considered “relative.” The Medical Services Commission of British Columbia has published a set of absolute contraindications to warfarin therapy, including the presence of severe or active bleeding diathesis, nonadherence to medication or INR monitoring, pregnancy, and allergy or intolerance to warfarin. The same set of guidelines lists a set of relative contraindications, including uncontrolled hypertension, severe liver disease, and recent surgery involving the nervous system,

Figure 1



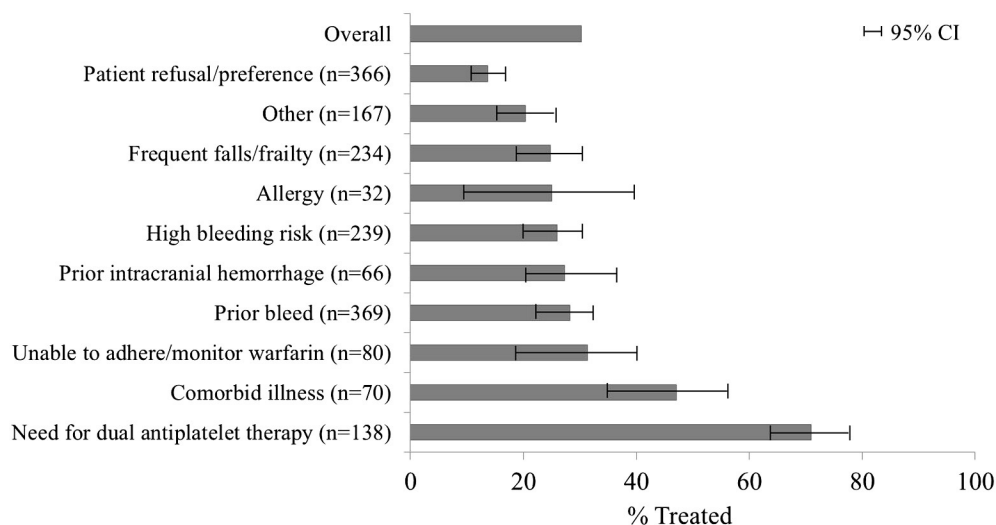
Factors associated with OAC contraindication documented at baseline. *Per 5% increase. †Per 10-mg/dL increase; linear spline with knot at 60 mg/dL. ‡Per 5-kg/m² increase; linear spline with knot at 34 kg/m². **Multivariable GEE estimates. Abbreviations: eGFR, estimated GFR; BMI, body mass index; Cog. Imp, cognitive impairment; AVN, atrioventricular node.

Figure 2



Factors associated with event-related OAC contraindication documented at baseline. *Per 5% increase. †Per 10-mg/dL increase; linear spline with knot at 60 mg/dL. **Multivariable GEE estimates. Abbreviations: eGFR, estimated GFR; BMI, body mass index; Cog. Imp, cognitive impairment; AVN, atrioventricular node.

Figure 3



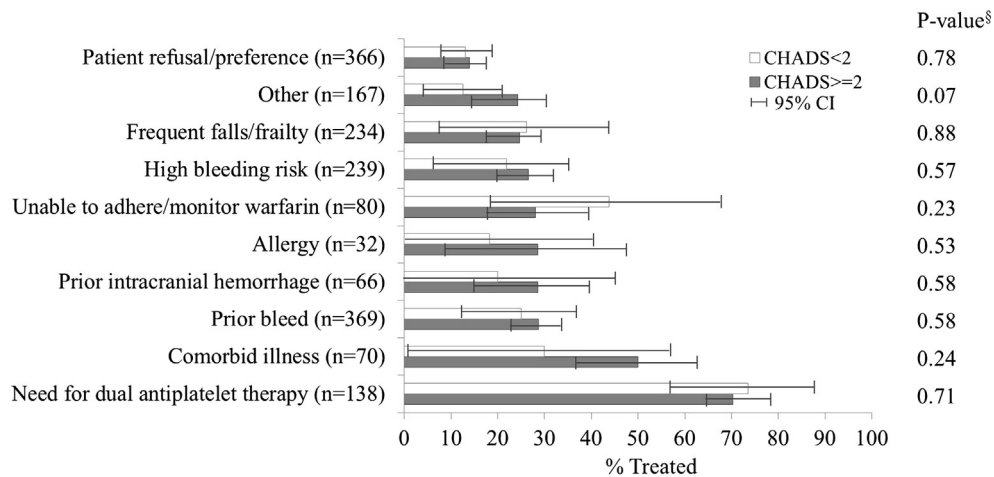
OAC* treatment rates within documented contraindication strata†. *Warfarin or dabigatran. †Contraindications not mutually exclusive.

spine, or eye, a number of which have been reported as absolute contraindications in other studies. Owing to this lack of consensus, we did not classify ORBIT-AF patients as having a relative or absolute contraindication to OAC. However, approximately 30.3% of patients with a documented contraindication to OAC therapy at baseline reported current OAC use, underscoring the likelihood that a substantial proportion of contraindications in ORBIT-AF are deemed by providers to be relative.

To further explore the relative nature of contraindications to OAC in clinical practice, we examined OAC treatment rates within each specific contraindication category. Understandably, we observed the lowest OAC treatment rates among patients with patient refusal or preference listed as the contraindication. The highest rates of OAC treatment were observed among patients for whom the listed contraindication included inability to adhere/monitor warfarin, comorbid illness, and need for dual antiplatelet therapy. Interestingly, treatment rates for prior bleed and prior intracranial hemorrhage, 2 contraindications that have been considered absolute in prior studies, were similar to or higher than treatment rates in more than half of the remaining contraindication categories. Given that OAC contraindication assessment is particularly relevant among those indicated for treatment, we assessed OAC treatment rates within each contraindication category stratified by patients with low stroke risk ($\text{CHADS}_2 < 2$) and patients with high stroke risk ($\text{CHADS}_2 \geq 2$). As expected, OAC treatment rates were higher among patients with high stroke risk for most contraindication categories. However, patients with low stroke risk had similar or slightly higher OAC treatment rates for contraindications due to prior bleed, high bleeding risk, inability to adhere/monitor, and

need for dual antiplatelet therapy. Besides patient preference/refusal, the lowest rate of OAC use in patients at high risk of stroke was among those considered as having frequent falls or being frail, despite prior work indicating that high fall risk is not an independent predictor of major bleeding on OAC.²¹ In all, these data highlight physician uncertainty in balancing contraindications vs indications for OAC in patients with AF.

A major challenge of implementing proper anticoagulation strategies in AF is the overlap between risk factors for bleeding and risk factors for stroke, evidenced by the large subpopulation of patients with both indications for and contraindications to OAC therapy. Investigators in the GARFIELD study reported underuse of anticoagulants among patients with high risk stroke ($\text{CHADS}_2 \geq 2$), largely due to perceived excess bleeding risk.²² In the ORBIT-AF population, patients with higher stroke risk ($\text{CHADS}_2 \geq 2$) were more likely to report event-related contraindications than patients in lower stroke risk categories, who were more likely to report contraindications due to patient preference. We also found a greater frequency of documented contraindications in patients older than 75 years, a finding consistent with prior studies. These findings underscore the complexity of OAC treatment decisions and the importance of both precise risk estimation and sound clinical judgment when balancing potential benefits and harms from anticoagulation in this subpopulation of high-risk patients.⁶ Because observed risk of stroke and major bleeding may differ from estimated risk at baseline, further exploration of clinical outcomes among patients with a documented contraindication who are treated with OAC is needed.

Figure 4

OAC* treatment rates within documented contraindication strata† by CHADS₂ risk score. *Warfarin or dabigatran. †Contraindications not mutually exclusive.

Limitations

A number of limitations to this analysis are worth noting. First, some patients enrolled in ORBIT-AF may have had OAC contraindications that were not documented in the medical record, and others may have had OAC contraindications documented that were not actually present. Second, there may be specific reasons for nontreatment that are not collected in ORBIT-AF and therefore would not be documented as contraindications. Third, there is likely an overlap between contraindication categories (eg, prior bleed and prior intracranial hemorrhage). Because these data are derived from a voluntary national registry, they are subject to potential limitations regarding site selection, patient selection, and generalizability. Fourth, although documented contraindications were collected separately from information on current treatment regimens, it is possible that the decision to treat influenced the reporting of a contraindication.

In conclusion, documented contraindications to OAC are common in an outpatient AF setting. The most frequently listed contraindications include prior bleed, high bleeding risk, patient refusal/preference, and frequent falls/frailty. Despite the presence of significant contraindications, many patients are prescribed anticoagulants, highlighting the challenge of balancing stroke and bleeding risks.

Disclosures

The ORBIT-AF registry is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ. This project was supported (in part) by funding from the Agency of Healthcare Research and Quality through cooperative

agreement number 1U19 HS021092. Dr. Singer was, in part, supported by the Eliot B. and Edith C. Shoolman fund of the Massachusetts General Hospital (Boston, MA).

This work was performed at the Duke Clinical Research Institute, Durham, NC.

Dr. O'Brien and Ms. Holmes report no disclosures. Dr. Ansell reports that he has received Consultant/Advisory Board fees from Bristol Myers Squibb, Pfizer, Janssen, Daiichi, Boehringer Ingelheim, Alere (all modest). Dr. Allen reports consulting fees from Amgen and J&J/Janssen. Dr. Hylek reports that she is a member of the Speakers Bureau (modest) for Boehringer-Ingelheim, Bayer and a member of the Consultant/Advisory Boards (Modest) for Johnson & Johnson, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Ortho-McNeil-Janssen. Dr. Kowey reports that he has served as a Consultant/Advisory Board for Boehringer Ingelheim, Bristol Myers Squibb, Johnson & Johnson, Portola, Merck, Sanofi, Daiichi Sankyo (all modest). Dr. Gersh reports that he is a member of the advisory board for Boston Scientific and St. Jude Medical (both modest). Dr. Fonarow reports that he has served as a Consultant/Advisory Board member for Ortho McNeil. Dr. Ezekowitz is a member of the speakers bureau with Boehringer Ingelheim and consultancy with Boehringer Ingelheim, ARYx Therapeutics, Pfizer, Sanofi, Bristol-Myers-Squibb, Portola, Daiichi Sankyo, Medtronic, Merck, Gilead, and Janssen. Mr. Koller reports no disclosures. Dr. Mahaffey has received research support from AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Portola, POZEN Pharmaceutical, Schering-Plough, and The Medicines Company, and has

consulting agreements with Amgen, AstraZeneca, Glaxo SmithKline, Johnson & Johnson, and Merck. Dr. Chang is an employee of Janssen. Dr. Peterson has received research support from Eli Lilly & Company and Janssen. Dr. Piccini has received research support from Boston Scientific Corporation and Janssen and consultancies to Forest Laboratories, Janssen, and Medtronic. Dr. Singer reports that he has received a research grant (significant) from Johnson and Johnson and served as a Consultant/Advisory Board member for Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Johnson and Johnson, Pfizer (modest) and Daiichi Sankyo (significant).

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8):983-8.
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(12):857-67.
3. O'Neil BJ, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med* 2010;123(7):638-45 e634.
4. Waldo AL, Becker RC, Tapson VF, et al. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. *J Am Coll Cardiol* 2005;46(9):1729-36.
5. Tulner LR, Van Campen JP, Kuper IM, et al. Reasons for under-treatment with oral anticoagulants in frail geriatric outpatients with atrial fibrillation: a prospective, descriptive study. *Drugs Aging* 2010;27(1):39-50.
6. Devereaux PJ, Anderson DR, Gardner MJ, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;323(7323):1218-22.
7. Gross CP, Vogel EW, Dhondt AJ, et al. Factors influencing physicians' reported use of anticoagulation therapy in nonvalvular atrial fibrillation: a cross-sectional survey. *Clin Ther* 2003;25(6):1750-64.
8. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. *Am Heart J* Oct 2011;162(4):606-612 e601.
9. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. *J Am Coll Cardiol* 2011;58(4):395-401.
10. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285(22):2864-70.
11. Lip GY, Nieuwlaet R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest* 2010;137(2):263-72.
12. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42(1):121-30.
13. Gladstone DJ, Bui E, Fang J, et al. Potentially preventable strokes in high-risk patients with atrial fibrillation who are not adequately anticoagulated. *Stroke* 2009;40(1):235-40.
14. Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Ann Intern Med* 1999;131(12):927-34.
15. Kalra L, Yu G, Perez I, et al. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000;320(7244):1236-9.
16. Samsa GP, Matchar DB, Goldstein LB, et al. Quality of anticoagulation management among patients with atrial fibrillation: results of a review of medical records from 2 communities. *Arch Intern Med* 2000;160(7):967-73.
17. Bradley BC, Perdue KS, Tisdell KA, et al. Frequency of anticoagulation for atrial fibrillation and reasons for its non-use at a Veterans Affairs medical center. *Am J Cardiol* 2000;85(5):568-72.
18. Flaker GC, McGowan DJ, Boechler M, et al. Underutilization of antithrombotic therapy in elderly rural patients with atrial fibrillation. *Am Heart J* 1999;137(2):307-12.
19. Mehra M. Impact of relative contraindications on the use, benefits, and risks of anticoagulant prophylaxis in atrial fibrillation: analysis of a claims database. *Open J Int Med* 2011;60-7.
20. Smith NL, Psaty BM, Furberg CD, et al. Temporal trends in the use of anticoagulants among older adults with atrial fibrillation. *Arch Intern Med* 1999;159(14):1574-8.
21. Donze J, Clair C, Hug B, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *Am J Med* 2012;125(8):773-8.
22. Kakkur AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One* 2013;8(5):e63479.

Appendix. Candidate variables for regression modeling

Age
Gender
Race
Education level
Geographic region
Heart failure
Prior stroke
Prior MI
Hypertension
Diabetes mellitus
Smoking
Obstructive sleep apnea
Dementia
AF type (first detected/new onset, paroxysmal, persistent, permanent)

Cardioversion
Implanted device
Catheter ablation of AF
AV node/HIS bundle ablation
AF ablation
Surgical/Hybrid maze
Body mass index
Heart rate
Systolic blood pressure
Rhythm on most recent 12-lead electrocardiogram
Evidence of left ventricular hypertrophy
Serum creatinine
Hematocrit