

# Residual stroke risk despite oral anticoagulation in patients with atrial fibrillation



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**BACKGROUND** Oral anticoagulation (OAC) reduces the risk of thromboembolic events in patients with atrial fibrillation (AF); however, thromboembolism (TE) still can occur despite OAC. Factors associated with residual risk for stroke, systemic embolism, or transient ischemic attack events despite OAC have not been well described.

**OBJECTIVE** The purpose of this study was to evaluate the residual risk of thromboembolic events in patients with AF despite OAC.

**METHODS** A total of 18,955 patients were analyzed in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF I and II) using multivariable Cox proportional hazard modeling. Mean age was  $72 \pm 10.7$ , and 42% were women. There were 451 outcome events.

**RESULTS** The risk of TE despite OAC increased with CHA<sub>2</sub>DS<sub>2</sub>-VASc score: 0.76 (95% confidence interval [CI] 0.63–0.92) events per 100 patient-years for CHA<sub>2</sub>DS<sub>2</sub>-VASc score <4 vs 2.01 (95% CI 1.81–2.24) events per 100-patient years for CHA<sub>2</sub>DS<sub>2</sub>-VASc score >4. Factors associated with increased risk were previous stroke or

transient ischemic attack (hazard ratio [HR] 2.87; 95% CI 2.30–3.59;  $P < .001$ ), female sex (HR 1.52; 95% CI 1.24–1.86;  $P < .001$ ), hypertension (HR 1.50; 95% CI 1.09–2.06;  $P = .01$ ), and permanent AF (HR 1.47; 95% CI 1.12–1.94;  $P = .001$ ). When transient ischemic attack was excluded, the results were similar, but permanent AF was no longer significantly associated with thromboembolic events.

**CONCLUSION** Patients with AF have a residual risk of TE with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score despite OAC. Key risk markers include previous stroke/transient ischemic attack, female sex, hypertension, and permanent AF.

**KEYWORDS** Atrial fibrillation; Oral anticoagulation; Residual risk; Stroke; Thromboembolism

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## KEY FINDINGS

- Patients with atrial fibrillation have a residual risk of stroke and transient ischemic attack that persists despite oral anticoagulation and is associated with traditional CHA<sub>2</sub>DS<sub>2</sub>-VASc risk factors in addition to other risk factors.
- Previous stroke/transient ischemic attack, female sex, hypertension, and permanent atrial fibrillation are the most significant risk factors associated with residual risk.
- Independent residual risk factors for stroke/transient ischemic attack were similar among different classes of anticoagulants.

## Introduction

Atrial fibrillation (AF) is a common arrhythmia with a lifetime risk >30%.<sup>1,2</sup> Patients with AF face a substantially increased risk of stroke and death.<sup>2</sup> Oral anticoagulation (OAC) reduces the risk of stroke and systemic embolism (SSE) in patients with AF. Despite the efficacy of direct-acting oral anticoagulants (DOACs) and warfarin in preventing stroke, patients treated with DOACs and warfarin have a continued risk of SSE of 1.1%–1.7% and 1.5%–2.2% per year, respectively, in previous trials.<sup>3–6</sup> Although it is clear that both warfarin and DOAC therapy substantially reduce the occurrence of SSE, there remains some degree of residual stroke risk despite treatment.<sup>7</sup> Although the residual risk of stroke in OAC-treated patients is comparatively low, its population burden remains high given the frequency of AF and the significant consequences of AF-related stroke. To define the magnitude of residual risk for SSE and transient ischemic attack (TIA) in clinical practice and to identify factors associated with residual risk despite OAC, we conducted a retrospective analysis of the US-based nationwide Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF I and II).

## Methods

### Study population

ORBIT-AF I and II are prospective, nationwide registries of incident and prevalent AF. ORBIT-I enrolled 10,137 patients from June 2010 to August 2011 from 176 outpatient sites across the United States. ORBIT-II enrolled 13,394 patients from February 2013 to July 2016 from 244 outpatient sites across the United States. Investigators followed these patients at 6-month intervals for 2–3 years. Inclusion criteria were documented electrocardiographic AF, age >18 years, and ability to provide consent and comply with expected follow-up appointments. Exclusion criteria included AF secondary to a known reversible condition, life expectancy <6 months, or solitary atrial flutter in isolation without AF. All patients were evaluated by a physician at enrollment and completed an AF symptom checklist. All subjects provided

written, informed consent. Patient data collection has been previously described in depth and utilized a case report form that included an extensive list of patient demographics, comorbidities, and medications.<sup>8,9</sup> All events were patient reported via questionnaire. All strokes were adjudicated with primary source documentation from the enrollment sites. Stroke or non-central nervous system SSE was the primary outcome and was defined as a new, sudden, focal neurologic deficit that persisted beyond 24 hours without an identifiable nonvascular cause.<sup>8</sup>

The purpose of this analysis was to identify risk factors for thromboembolic events (ie, SSE+TIA) among patients with AF already receiving therapeutic anticoagulation. We evaluated 10,137 patients from ORBIT-AF and 13,394 patients from ORBIT-AF II. Patients were excluded if they were not taking any OAC at baseline (n = 3982), were receiving both warfarin and DOAC therapy (n = 6), or had no available follow-up (n = 588).

### Statistical analysis

Baseline characteristics by incident thromboembolism (TE) are given frequency (percentage) for categorical variables and mean ± SD for continuous variables (Table 1). Patient characteristics at baseline were compared using the  $\chi^2$  test for categorical variables and the Student *t* test for continuous variables. When describing the rates of TE in the overall cohort and according to CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, we calculated the number of events per 100 patient-years and the 95% confidence interval (CI). We performed the same calculations after separating patients by concomitant anticoagulation and antiplatelet therapy compared with anticoagulation alone.

We performed a multivariable Cox proportional hazard model to identify factors independently associated with TE in AF patients receiving anticoagulation. A complete list of candidate covariates is given in the Supplemental Appendix. Backward selection was used for variable selection, with an  $\alpha$  of 0.05 required for a covariate to remain in the model. Missing data were accounted for in the backward selection using the first imputation from 5 multiply imputed datasets obtained using Markov chain Monte Carlo simulation or regression methods. All continuous variables were tested for linearity, and any nonlinear relationships were accounted for using linear splines. With the final list of covariates from the backward selection results, the model was run again, including a robust covariance estimate to account for the correlation within site. Results from the 5 imputed datasets were combined. The hazard ratio (HR) for TE, corresponding 95% CI, and *P* value are presented for each factor. All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

All participating sites in the ORBIT-AF I and ORBIT-AF II registries obtained institutional review board approval, including Duke Institutional Review Board approval, before patient recruitment. Patients provided written informed consent and were not compensated for their participation. The research reported adhered to relevant ethical guidelines, including the Helsinki Declaration as revised in 2013.

**Table 1** Baseline characteristics according to occurrence of TE

	Overall (N = 18,955)	No TE (N = 18,504)	TE (N = 451)	P value
Age (y)	72 ± 10.7	72 ± 10.7	76 ± 9.7	<.001
Male	11,026 (58.2)	10,821 (58.5)	205 (45.5)	<.001
Race				
White	16,599 (87.6)	16,198 (87.6)	401 (88.9)	.91
Black	893 (4.7)	872 (4.7)	21 (4.6)	
Hispanic	907 (4.8)	891 (4.8)	16 (3.6)	
Medical history				
Current smoker	1181 (6.2)	1155 (6.2)	26 (5.8)	.15
Former smoker	7829 (41.3)	7624 (41.2)	205 (45.5)	
Recent smoker	120 (0.6)	115 (0.6)	5 (1.1)	
Hypertension	15,696 (82.8)	15,290 (82.6)	406 (90.0)	<.001
Obstructive sleep apnea	3475 (18.3)	3384 (18.3)	91 (20.2)	.31
Hyperlipidemia	13,100 (69.1)	12,775 (69.0)	325 (72.1)	.17
Diabetes	5379 (28.4)	5239 (28.3)	140 (31.0)	.20
GI bleed	1067 (5.6)	1029 (5.6)	38 (8.4)	.009
Congestive heart failure	5162 (27.2)	5008 (27.1)	154 (34.2)	.001
NYHA functional class III	980 (5.2)	947 (5.1)	33 (7.3)	.006
NYHA functional class IV	79 (0.4)	78 (0.4)	1 (0.2)	
Peripheral vascular disease	1974 (10.4)	1886 (10.2)	88 (19.5)	<.001
Previous CVA	2618 (13.8)	2452 (13.3)	166 (36.8)	<.001
Previous stroke	1469 (7.8)	1372 (7.4)	97 (21.5)	<.001
Previous TIA	1337 (7.1)	1236 (6.7)	101 (22.4)	<.001
History of CAD	5834 (30.8)	30.6)	182 (40.4)	<.001
Previous myocardial infarction	2371 (12.5)	2281 (12.3)	90 (20.0)	<.001
Weight (kg)	91.3 ± 25.0	91.4 ± 25.1	84.1 ± 23.4	<.001
Heart rate (bpm)	74.0 ± 15.8	74.0 ± 15.8	75.0 ± 16.6	.19
Systolic BP (mm Hg)	127.2 ± 17.2	127.2 ± 17.3	128.6 ± 17.0	.09
Diastolic BP (mm Hg)	74.0 ± 10.9	74.0 ± 10.9	73.5 ± 11.4	.37
eGFR (mL/min/1.73 m <sup>2</sup> )	70 (56, 86)	70 (56, 86)	65 (52, 78)	<.001
AF type				
First detected/new onset	5538 (29.2)	5446 (29.4)	92 (20.4)	<.001
Paroxysmal	7546 (39.8)	7376 (39.9)	170 (37.7)	
Persistent	2897 (15.3)	2845 (15.4)	52 (11.5)	
Permanent	2972 (15.7)	2835 (15.3)	137 (30.4)	
AF management				
Rate	12242 (64.7)	11919 (64.5)	323 (71.6)	.002
Rhythm	6694 (35.4)	6566 (35.5)	128 (28.4)	
Statin therapy	10,172 (53.7)	10,015 (53.6)	157 (57.5)	.20
Antithrombotic medications				
Aspirin	5684 (30.0)	5502 (29.7)	182 (40.4)	<.001
Warfarin	8745 (46.1)	8471 (45.8)	274 (60.8)	<.001
Clopidogrel	739 (3.9)	715 (3.9)	24 (5.3)	.11
Prasugrel	15 (<0.1)	15 (<0.1)	0 (0)	.55
Ticagrelor	17 (<0.1)	16 (<0.1)	1 (0.2)	.34
Aggrenox	12 (<0.1)	12 (<0.1)	0 (0)	.59
Dabigatran	1113 (5.9)	1086 (5.9)	27 (6.0)	.92
Rivaroxaban	4702 (24.8)	4618 (25.0)	84 (18.6)	.002
Apixaban	4288 (22.6)	4225 (22.8)	63 (14.0)	<.001
Edoxaban	107 (0.6)	104 (0.6)	3 (0.7)	.77
CHADS-VASc score				
0	458 (2.4)	457 (2.5)	1 (0.2)	<.001
1	1499 (7.9)	1484 (8.0)	15 (3.3)	
2	2845 (15.0)	2816 (15.2)	29 (6.4)	
3	4053 (21.4)	3992 (21.6)	61 (13.5)	
4	4387 (23.2)	4296 (23.2)	91 (20.2)	
5	3108 (16.4)	3020 (16.3)	88 (19.5)	
6	1580 (8.3)	1501 (8.1)	79 (17.5)	
7	709 (3.7)	649 (3.5)	60 (13.3)	
8	260 (1.4)	237 (1.3)	23 (5.1)	
9	55 (0.3)	51 (0.3)	4 (0.9)	

Values are given as mean ± SD, n (%), or mean (25th, 75th percentiles) unless otherwise indicated.

AF = atrial fibrillation; BP = blood pressure; CAD = coronary artery disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; NYHA = New York Heart Association; TE = thromboembolism; TIA = transient ischemic attack.

**Table 2** Rates of residual risk of thromboembolism

CHADS-VASc score	All OAC (N = 18,954)		OAC without antiplatelet (N = 12,847)		OAC with antiplatelet (N = 6107)	
	No. of events	Event rate	No. of events	Event rate	No. of events	Event rate
0–1 (N = 1957)	16	0.56 (0.34, 0.91)	12	0.53 (0.30, 0.94)	4	0.65 (0.24, 1.72)
2 (N = 2845)	29	0.65 (0.45, 0.94)	18	0.54 (0.34, 0.86)	11	0.99 (0.55, 1.79)
3 (N = 4053)	61	0.92 (0.72, 1.19)	41	0.90 (0.66, 1.22)	20	0.98 (0.64, 1.53)
4 (N = 4387)	91	1.23 (1.00, 1.51)	51	1.08 (0.82, 1.42)	40	1.50 (1.10, 2.04)
5 (N = 3108)	88	1.67 (1.36, 2.06)	54	1.70 (1.30, 2.22)	34	1.63 (1.17, 2.28)
6 (N = 1580)	79	2.88 (2.31, 3.58)	34	2.15 (1.54, 3.01)	45	3.86 (2.88, 5.16)
7+ (N = 1024)	87	4.98 (4.04, 6.15)	44	4.81 (3.58, 6.47)	43	5.16 (3.83, 6.96)
Overall	451	1.45 (1.32, 1.59)	254	1.24 (1.09, 1.40)	197	1.87 (1.63, 2.15)

Event rates are given per 100 patient-years.

OAC = oral anticoagulation.

## Results

### Patient characteristics

A total of 18,955 patients receiving OAC with at least 1 follow-up visit were analyzed. The characteristics of the cohort according to the occurrence of TE are listed in [Table 1](#). [Supplemental Tables 1](#) and [Table 2](#) list the characteristics of the DOAC and warfarin groups, respectively. [Supplemental Table 3](#) lists the baseline characteristics when separating SSE and TIA events. The majority of the population (86%) had CHA<sub>2</sub>DS<sub>2</sub>-VASc scores ranging from 0–5. There was a similar distribution of patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc <4 (47%) and those with a score ≥4 (53%). Associated risk factors associated with the occurrence of TE included previous stroke/TIA, female sex, hypertension, permanent AF, antiplatelet use, chronic obstructive pulmonary disease (COPD), previous myocardial infarction (MI), renal dysfunction, and older age.

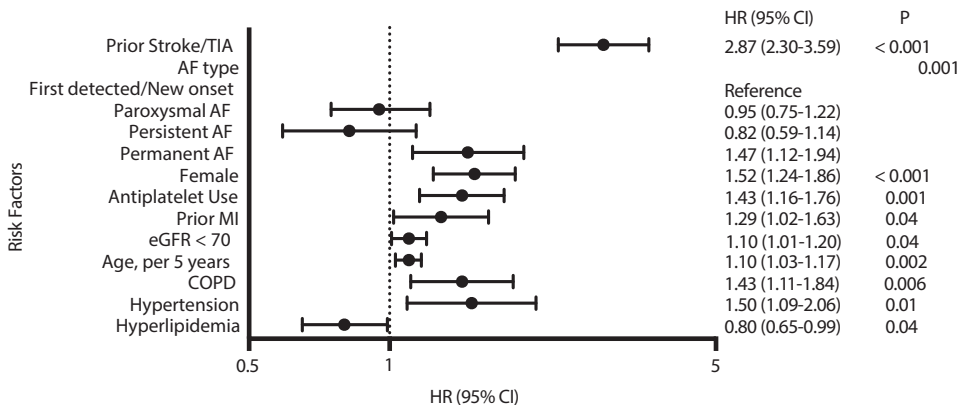
### Anticoagulation

OAC included warfarin (46.1%), rivaroxaban (24.8%), apixaban (22.6%), dabigatran (5.9%), and edoxaban (0.6%) ([Table 1](#)). Concomitant aspirin therapy was used by 30% of the population. Other antiplatelet therapy was used only in a small minority of the patients (clopidogrel 3.9%, prasugrel <0.1%, ticagrelor <0.1%, and aspirin/dipyridamole [Aggrenox, Boehringer Ingelheim] <0.1%).

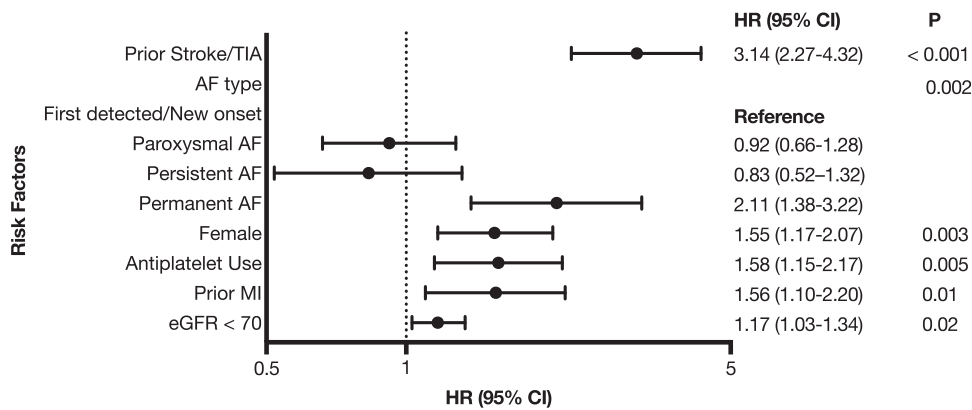
### Frequency of TE

A total of 451 thromboembolic events occurred in a total population of 18,955 patients. Overall the rate of TE in the entire cohort despite OAC was 1.45 per 100-patient years (95% CI 1.32–1.59). TE rates stratified by CHA<sub>2</sub>DS<sub>2</sub>-VASc score are given in [Table 2](#). [Supplemental Tables 4](#) and [5](#) list TE rates separated between DOAC and warfarin subgroups, respectively. [Supplemental Table 6](#) shows residual risk of SSE only excluding TIA among all OAC. There was an increase in the event rate per 100 patient-years with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc scores <4 had event rates of 0.76 (95% CI 0.63–0.92) per 100 patient-years, whereas those with scores ≥4 had 2.01 (95% CI 1.81–2.24) events per 100 patient-years. There was an increased unadjusted incidence of TE in the patients with concomitant antiplatelet use of 1.87 (95% CI 1.63–2.15) events per 100 patient-years compared with those who used OAC monotherapy with an event rate of 1.24 (95% CI 1.09–1.40) per 100 patient-years.

Independent factors associated with TE despite OAC were previous stroke or TIA, female sex, hypertension, permanent AF, antiplatelet use, COPD, previous MI, age, and renal dysfunction ([Figure 1](#)). Independent factors associated with TE despite DOAC and warfarin therapy are shown in [Figures 2](#) and [3](#), respectively. Previous stroke/TIA had the strongest association with developing TE while receiving



**Figure 1** Independent factors associated with thromboembolism despite oral anticoagulation (direct-acting oral anticoagulation or warfarin). AF = atrial fibrillation; CI = confidence interval; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; TIA = transient ischemic attack.



**Figure 2** Independent factors associated with thromboembolism despite direct-acting oral anticoagulation. Abbreviations as in Figure 1.

anticoagulation therapy (HR 2.87; 95% CI 2.30–3.59;  $P < .001$ ). Female sex and hypertension had moderately strong associations (HR 1.52; 95% CI 1.24–1.86;  $P < .001$ ; and HR 1.50; 95% CI 1.09–2.06;  $P = .01$ , respectively). Permanent AF compared with paroxysmal, persistent, or new-onset AF had a moderately strong association with TE despite OAC (HR 1.47; 95% CI 1.12–1.94;  $P = .001$  relative to new-onset AF). Interestingly, antiplatelet use had an association with higher rates of TE (HR 1.43; 95% CI 1.16–1.76;  $P = .001$ ). Other factors associated with a higher risk of TE were COPD (HR 1.43; 95% CI 1.11–1.84;  $P = .006$ ), previous MI (HR 1.29; 95% CI 1.02–1.63;  $P = .04$ ), renal dysfunction (HR 1.10; 95% CI 1.01–1.20;  $P = .04$ ), and increasing age (HR 1.10; 95% CI 1.03–1.17;  $P = .002$  for every 5 years of age).

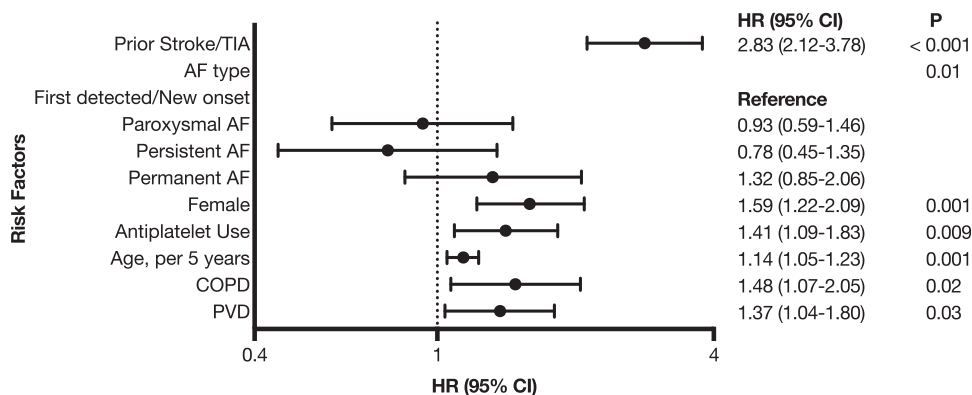
factor for stroke alone in both the DOAC (HR 2.51; 95% CI 1.66–3.79) and warfarin (HR 2.59; 95% CI 1.89–3.53) subgroups. Interestingly, peripheral vascular disease (HR 2.51; 95% CI 1.66–3.79) and severe atrial enlargement (HR 2.31; 95% CI 1.32–4.03) emerged as risk factors in the DOAC only subgroup. To further assess the association between continuous  $CHA_2DS_2-VASc$  score and SSE, a sensitivity analysis was performed. The models included a robust covariance estimate to account for correlation within site. Both unadjusted and adjusted models were applied, with the adjusted model accounting for antiplatelet use. The results of the 2 models were almost identical (unadjusted model: HR 1.43; 95% CI 1.36–1.51; adjusted model for antiplatelet use: HR 1.42; 95% CI 1.35–1.50).

**Sensitivity analyses regarding stroke only**

To assess whether independent factors were associated with stroke vs TIA, a sensitivity analysis was performed on all available variables for OAC, DOAC and warfarin subgroups. Supplemental Figure 1 shows the factors most associated with stroke only despite OAC: previous stroke/TIA (HR 2.48; 95% CI 1.89–3.26) and current smoking status (HR 2.05; 95% CI 1.26–3.35). Permanent AF did not emerge as an associated risk factor when TIAs were excluded. Supplemental Figures 2 and Figure 3 shows identified factors associated with stroke only with DOAC therapy and warfarin monotherapy. Previous stroke/TIA was a significant independent risk

**Predictors of TE in high-risk patients**

To examine predictors of TE despite OAC in high-risk patients, we analyzed a subset of the cohort with  $CHA_2DS_2-VASc$  score  $\geq 4$ , and a different set of covariates emerged (Supplemental Figure 4). Previous stroke/TIA remained the strongest factor associated with TE among those patients at high risk (HR 2.86; 95% CI 2.21–3.70;  $P < .001$ ), and current smoking status emerged as the second strongest associated factor (HR 2.12; 95% CI 1.31–3.42;  $P = .002$ , relative to non-smokers). Hypertension and female sex remained moderately associated (HR 1.79; 95% CI 1.11–2.90;  $P = .02$ ; and HR 1.47; 95% CI 1.14–1.90;  $P = .003$ , respectively). Antiplatelet



**Figure 3** Independent factors associated with thromboembolism despite warfarin. PVD = peripheral vascular disease; other abbreviations as in Figure 1.



use remained associated with a higher risk for TE (HR 1.45; 95% CI 1.14–1.84;  $P = .002$ ). Severe enlargement of the left atrium emerged as a moderately strong associated factor (HR 1.50; 95% CI 1.09–2.05;  $P = .008$ , relative to normal left atrial diameter). COPD, previous MI, and renal dysfunction no longer shared a statistically significant association.

## Discussion

In this analysis of a contemporary nationwide AF registry, we defined the rates of TE despite OAC as well as important factors independently associated with residual risk of stroke. The 3 major findings of our analysis are as follows. First, the overall rate of TE despite OAC remains significant in patients with high CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and is consistent with results of previous clinical trials of DOACs.<sup>10–13</sup> Second, CHA<sub>2</sub>DS<sub>2</sub>-VASc scores continue to risk-stratify patients receiving OAC. Third, several notable risk factors are associated with TE despite OAC, including previous stroke/TIA, female sex, hypertension, and type of AF.

OAC effectively reduces the risk of stroke and improves survival in patients with AF. Despite the efficacy of OAC for preventing stroke, patients successfully treated with OAC have a residual risk of SSE between 1% and 2% per year in previous trials.<sup>3–6</sup> However, in higher-risk subgroups the rate of SSE despite OAC seems to be much higher. For example, in patients with AF, previous stroke, and creatinine clearance <60 mL/min, the risk of SSE approaches 4% per year, and this excludes TIAs.<sup>14</sup> In our analysis, the overall event rate of TE in patients treated with OAC was 1.45 events per 100 patient-years. Moreover, there was a significant increase in the residual risk of TE with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc scores have been shown in retrospective cohort studies to be associated with an increased risk for cardiovascular hospitalization in AF.<sup>15</sup>

Our study was inclusive with regard to what defines OAC success and evaluated risk factors associated with both SSE and TIA. These results demonstrate that opportunity remains to further optimize clinical outcomes in AF, especially in those with a high residual stroke risk. The risk of TE might be reduced with emerging novel anticoagulants and devices along with lifestyle modification. For example, factor XI inhibitors may have a role in treating residual risk.<sup>16</sup> Alternatively, combination therapy with DOAC and left atrial appendage closure also might have a role in patients with very high residual risk. A combined approach (so-called “belt and suspenders”) using left atrial appendage occlusion and OAC resulted in significant reduction of stroke in the LAAOS (Left Atrial Appendage Occlusion Study) III trial.<sup>17</sup> These hypotheses should be explored and tested in future clinical trials. Risk factor modification also is important. Many of these risk factors can be improved through lifestyle modifications, such as smoking cessation, blood pressure management, and weight loss. Despite obesity being an independent risk factor for development of AF, it did not emerge as an associated risk factor for residual stroke risk.

It is important to identify which patients are at highest risk for TE despite OAC so that their risk factors can be modified.

In the entire cohort receiving OAC, the strongest risk factors for TE were (1) previous stroke/TIA; (2) female sex; (3) hypertension; and (4) permanent AF. Previous stroke is a known and potent risk factor for recurrent stroke. Whether there is a greater risk for TE with persistent AF compared to paroxysmal AF is controversial, although data from pivotal DOAC trials and from ENGAGE AF TIMI-48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48) suggest that this may be the case.<sup>18–20</sup> Our results are consistent with these observations, with permanent AF sharing a stronger association with TE than paroxysmal or persistent AF. COPD, previous MI, and age also were associated with TE. Interestingly, antiplatelet use also was associated with TE despite OAC. This association was present in analysis of both the entire cohort and the higher-risk patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$ . This is an important association because many physicians consider the addition of aspirin therapy to DOAC treatment in patients at higher risk, but this may have a detrimental effect. The unexpected association between antiplatelet use and higher stroke risk may be secondary to nonembolic stroke risk. Although we adjusted for vascular disease in the analysis, these factors may contribute more significantly than previously anticipated. TE would not be reduced with OAC if aspirin were a confounder for atherosclerotic plaque emboli etiology. Antiplatelet use may contribute to an increased bleeding risk without a reduction in ischemic stroke risk. OAC has been proven to significantly reduce the frequency of SSE in patients with AF, so it is important that patients be encouraged to optimize lifestyle risk factors that likely also contribute to increased risk of TE in those with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. Higher-risk patients require more aggressive monitoring and treatment of modifiable risk factors, such as tobacco use and anticoagulation adherence.

When we analyzed a subset of the cohort with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$ , a different set of risk factors emerged. The goal of this analysis was to evaluate whether independent risk factors for TE were different in patients at highest risk. Previous stroke/TIA, female sex, hypertension, permanent AF, age, and antiplatelet use remained as associated risk factors; however, other factors such as current and recent/former smoking status and severe left atrial enlargement emerged. One consideration is whether the increased residual risk for TE with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score is related to a modifiable risk of AF or a nonmodifiable risk unrelated to AF, such as that of nonembolic stroke risk or underlying atherosclerotic disease. The residual risk for TE may result from comorbidities independent of AF. However, the majority of associated risk factors are also risk factors for AF alone and therefore likely contribute to direct modifiable AF-related risk. The emergence of associated antiplatelet use as a risk factor in both groups analyzed does raise the question as to how much underlying atherosclerotic disease contributes to residual stroke risk and whether the risk analyzed is predominately cardioembolic. Although the vast majority of stroke events in patients with AF are cardioembolic, it is estimated that 13% are lacunar strokes due to small vessel intracranial disease.<sup>21</sup> However, a

known diagnosis of coronary artery disease did not emerge as a statistically significant risk factor in our analysis.

It is important to consider that adherence may contribute to residual risk. We would expect higher residual risk in patients with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores regardless of adherence because their baseline risk is much higher. If adherence is similar across groups, then the relative risk reduction may be the same across CHA<sub>2</sub>DS<sub>2</sub>-VASc scores; however, the residual risk remains higher because the increased potential benefit of OAC in these higher-risk groups is limited more significantly by adherence than in the groups with lower CHA<sub>2</sub>DS<sub>2</sub>-VASc scores. Programs such as Get With The Guidelines-AFIB (GWTG-AFIB) are essential to improving OAC adherence and have been shown to increase prescription rates to >90% in AF patients discharged from the hospital.<sup>22</sup> In clinical practice, patients should not be categorized based on CHA<sub>2</sub>DS<sub>2</sub>-VASc scores  $\geq 2$  alone but instead evaluated along a continuum of risk. Our analysis successfully identified a higher-risk subset of patients with AF; however, further studies are needed to determine the contribution of AF compared to non-AF-related risk factors contributing to the increased risk of TE.

### Study limitations

The results of this observational analysis identified risk factors and are hypothesis-generating. However, several limitations to this study should be considered. The most important limitation is the inability to monitor patient adherence. Specifically, there is no measure of DOAC adherence routinely captured in clinical practice or in the ORBIT registry. We were unable to differentiate between embolic and nonembolic/vascular strokes and cannot confirm that all strokes were secondary to thromboembolic events related to AF. Our inability to differentiate whether events were causally related to AF limits the ability to determine whether more aggressive therapies such as atrial appendage occlusion devices would be beneficial in these high-risk patients. Although the primary analysis included stroke and TIA, sensitivity analyses focused on stroke alone, and excluding TIA as an endpoint largely yielded similar results. Antiplatelet use was shown to be a statistically significant predictor of TE when assessed in both the entire patient population and when stratified by CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 4$ . Although concomitant antiplatelet use may contribute to increased risk for hemorrhagic stroke, it may also be a confounding factor that represents patients with more comorbid disease (eg, more advanced atherosclerotic disease).

### Conclusion

Patients with AF have a continuum of residual risk of stroke and TIA that increases with higher CHA<sub>2</sub>DS<sub>2</sub>-VASc score despite adequate anticoagulation. Previous stroke/TIA, female sex, hypertension, and permanent AF are the most prominent predictors of stroke and TIA. Other predictors include antiplatelet use, COPD, previous MI, and increasing age. Assessment of residual risk will become more important as additional stroke prevention technologies and pharmacotherapies

become available. Randomized trials are needed to assess whether patients with higher residual risk of stroke and TIA would benefit from adjunctive or novel preventive strategies.

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### Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2022.09.018>.

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