ORIGINAL RESEARCH

Stroke Risk and Treatment in Patients with Atrial Fibrillation and Low CHA_2DS_2-VASc Scores: Findings From the ORBIT-AF I and II Registries

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Background—Current American College of Cardiology/American Heart Association guidelines suggest that for patients with atrial fibrillation who are at low risk for stroke ($CHA_2DS_2VASc=1$) (or women with $CHA_2DS_2VASc=2$) a variety of treatment strategies may be considered. However, in clinical practice, patterns of treatment in these "low-risk" patients are not well described. The objective of this analysis is to define thromboembolic event rates and to describe treatment patterns in patients with low-risk CHA_2DS_2VASc scores.

Methods and Results—We compared characteristics, treatment strategies, and outcomes among patients with a $CHA_2DS_2VASc=0$, $CHA_2DS_2VASc=1$, females with a $CHA_2DS_2VASc=2$, and $CHA_2DS_2VASc \geq 2$ in ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) I & II. Compared with $CHA_2DS_2VASc \geq 2$ patients (84.2%), those with a $CHA_2DS_2VASc=0$ (60.3%), 1 (69.9%), and females with a CHA_2DS_2VASc score=2 (72.4%) were significantly less often treated with oral anticoagulation ($P<0.0001$). Stroke rates were low overall and ranged from 0 per 100 patient-years in those with $CHA_2DS_2VASc=0$, 0.8 (95% confidence interval [CI] [0.5–1.2]) in those with $CHA_2DS_2VASc=1$, 0.8 (95% CI [0.4–1.6]) in females with a CHA_2DS_2VASc score=2, and 1.7 (95% CI [1.6–1.9]) in $CHA_2DS_2VASc \geq 2$. All-cause mortality (per 100 patient-years) was highest in females with a CHA_2DS_2VASc score=2 (1.4) (95% CI [0.8–2.3]), compared with patients with a $CHA_2DS_2VASc=0$ (0.2) (95% CI [0.1–1.0]), and $CHA_2DS_2VASc=1$ (1.0) (95% CI [0.7–1.4]), but lower than patients with a $CHA_2DS_2VASc \geq 2$ (5.7) (95% CI [5.4–6.0]).

Conclusion—The majority of CHA_2DS_2VASc=0-1 patients are treated with oral anticoagulation. In addition, the absolute risks of death and stroke/transient ischemic attack were low among both male and females CHA_2DS_2VASc=0-1 as well as among females with a CHA_2DS_2VASc score=2.

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Key Words: oral anticoagulation • Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) • stroke

Atrial fibrillation (AF) is associated with a significantly increased risk of stroke and systemic embolism, which varies based upon the presence of additional risk factors.[1–3] Patients with AF-related strokes have worse prognosis and higher risk of recurrent events compared with non-AF-related strokes.[4] Prevention of stroke and systemic embolism is facilitated through the use of antithrombotic agents, principally oral vitamin K-antagonists or direct OACs (oral

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Accompanying Data S1, Tables S1 through S7, and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008764

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Clinical Perspective

What Is New?

- Among patients with low CHA_2DS_2-VASc scores, the majority were treated with systemic oral anticoagulation.
- Aspirin use was high among patients with low CHA_2DS_2-VASc scores, even in those already treated with oral anticoagulation at baseline.

What Are the Clinical Implications?

- The absolute risk of death and stroke/transient ischemic attack was low among both males and females CHA_2DS_2-VASc=0-1 as well as among females with a CHA_2DS_2VASc score=2.

anticoagulants).[5–8] The CHA_2DS_2VASc score is a risk stratification tool used to estimate the risk of stroke in patients with nonvalvular AF[9] and is recommended for use in the guidelines of many international cardiovascular medicine societies.[10,11]

Differences exist in the treatment recommendations and administration of oral anticoagulation for "low risk" patients across various guidelines. At present the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines for the management of AF recommend that patients with a CHA_2DS_2VASc score=1 can be treated with no therapy, aspirin only, or oral anticoagulation (Class IIb, Level of Evidence C); for patients with a CHA_2DS_2VASc score=0, antiplatelet or OAC therapy can be omitted (class IIa).[10] The European guidelines favor treatment in patients with 1 nonsex risk factor.[12,13] The true absolute risk and optimal treatment in these patients, including females with a CHA_2DS_2-VASc score=2, is controversial and not entirely known.[14] Accordingly, we used the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) I and II to define thromboembolic event rates in "low"-risk patients in contemporary community practice and to describe the antiplatelet and anticoagulant treatment patterns of patients with a CHA_2DS_2-VASc score=0, 1 (by definition) and females with a CHA_2DS_2-VASc=2 (females with 1 additional stroke risk factor).

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 rationale and design of the ORBIT-AF and ORBIT-AF II registries have been previously described.[15,16] Both ORBIT-AF and OBRIT-AF II are prospective, nationwide multicenter registries of patients with AF across the United States managed by a variety of providers including internists, general cardiologists, and electrophysiologists. Briefly, eligible patients included those 18 years of age or older, with electrocardiographically documented AF, who were able to provide written informed consent, and to comply with regularly scheduled follow-up visits. Patients with atrial flutter only and those with reversible causes of AF (eg, pulmonary embolism) were excluded from participation. As ORBIT-AF and ORBIT-AF II are observational registries, all treatment decisions were left to the discretion of the individual treating physicians in accordance with practice guidelines, recommendations, and local standards of care. Following initial enrollment, longitudinal information was collected during healthcare visits at ≈6-month intervals up to 36 months (6-month intervals up to 24 months for ORBIT-AF II). These follow-up data included information on hospitalizations, bleeding events, quality of life, procedures, and medical therapies. ORBIT-AF I included patients with AF that was not thought to be attributable to a reversible cause. By design, ORBIT-AF II also excluded patients with reversible causes of AF (eg, pulmonary embolism). Enrollment in ORBIT-AF II was geared toward capturing a contemporary cohort of patients with AF treated with direct OACs (dabigatran, apixaban, rivaroxaban, and edoxaban); only patients with either (1) new-onset AF within the previous 6 months and/or (2) patients with AF recently switched to a direct OAC within 3 months were eligible.

For the purpose of this analysis, we identified patients at "low" risk of thromboembolic stroke based upon guideline recommendations, including those with a CHA_2DS_2VASc score of zero, 1 (by definition), and females with a CHA_2DS_2VASc score=2, with our comparison group being patients with a CHA_2DS_2VASc ≥2 (excluding females with CHA_2DS_2VASc score=2).[10,12] Between June 29, 2010 and August 9, 2011, 10 137 patients were enrolled in the ORBIT-AF registry from 176 sites across the United States. From this we excluded 388 patients because of incomplete follow-up or death without any follow-up (postbaseline). This yielded a final study population of 9749 from which CHA_2DS_2VASc risk scores were calculated. Among these 9749 patients, at enrollment 212 (2.1%) had a CHA_2DS_2VASc score of 0, 659 (6.8%) had a CHA_2DS_2VASc score of 1, and 267 (2.7%) females had a CHA_2DS_2VASc score=2. Between February 20, 2013 and June 8, 2016, 11 603 patients were enrolled in the ORBIT-AF II registry from 242 sites across the United States. From this we excluded 2954 because of incomplete follow-up or death without any follow-up. This yielded a final study population of 8649. Among these 8649 patients, at enrollment 329 (4.0%) had a CHA_2DS_2VASc score of 0, 930 (11.0%) had a CHA_2DS_2VASc score of 1, and 403 (4.7%) females had a CHA_2DS_2VASc score=2.

Statistical Analysis

We compared baseline and AF characteristics of patients between 4 groups: $CHA_2DS_2VASc=0$, $CHA_2DS_2VASc=1$, females with a CHA_2DS_2VASc score=2, and all patients with a $CHA_2DS_2VASc \geq 2$ (excluding females with a CHA_2DS_2VASc score=2). Continuous variables were presented as medians (interquartile range) and categorical variables will be presented as proportions. To compare characteristics between groups, we used the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. In order to describe the major outcomes for patients with $CHA_2DS_2VASc=0$, CHA_2DS_2-VASc=1, and females with a CHA_2DS_2VASc score=2, we calculated the total number of events and number per 100 patient-years for the overall group and 3 stratified groups. In addition, adjusted and unadjusted rates of major outcomes alone and major outcomes stratified by OAC use were performed using Cox proportional hazard modeling using Firth's penalized likelihood method, respectively. For the adjusted analysis, the model was composed of several covariates including prior atrioventricular node/HIS bundle ablation, AF type, age, anemia, prior antiarrhythmic drug use, prior percutaneous coronary intervention, BMI, cancer, cognitive impairment/dementia, chronic obstructive pulmonary disease, history of coronary artery disease, diabetes mellitus, diastolic blood pressure, systolic blood pressure, dialysis, eGFR, European Heart Rhythm Association score, sex, New York Heart Association functional status, frailty, height, history of drug abuse, history of gastrointestinal bleed, hyperlipidemia, hypertension, insurance status, intraventricular conduction, hematocrit, left atrial diameter type, liver disease, level of education, left ventricular ejection fraction type, obstructive sleep apnea, prior myocardial infarction, family history of AF, significant valvular disease, heart rate, peripheral vascular disease, rhythm control, smoking status, provider specialty, history of stroke/transient ischemic attack (TIA), and weight. For the unadjusted analysis, interaction testing was performed to test the association between the outcome and therapy within each CHA_2DS_2VASc group.

The ORBIT-AF and ORBIT-AF II registries were approved by the Duke Institutional Review Board, and all participating sites obtained institutional review board approval pursuant to local requirements. All subjects provided written, informed consent. All *P* values presented are 2 sided. All statistical analyses were performed at the Duke Clinical Research Institute using SAS software (version 9.3; SAS Institute, Cary, NC).

Results

Patient and AF Characteristics

In the overall cohort (ORBIT AF I & II) CHA_2DS_2VASc 0-1 or females with a CHA_2DS_2VASc score=2 accounted for 15.2% (N=2820/18 398) of the overall population (Table 1). The majority of patients with a CHA_2DS_2-VASc score=0 and 1 were 50 years and older (Figure S1 and Figure 1), respectively. Compared with patients with a CHA_2DS_2VASc score ≥ 2 (excluding females with an additional stroke risk factor), patients with a CHA_2DS_2VASc score=0, CHA_2DS_2VASc score=1, and females with a CHA_2DS_2VASc score=2 were younger, more likely to have paroxysmal AF, more likely to be treated with a rhythm control strategy including the use of antiarrhythmic drugs and catheter ablation of AF, more likely to have disabling or severe symptoms associated with AF, and less likely to have risk factors associated with AF such as hypertension, diabetes mellitus, or coronary artery disease (Table 1).

Stroke Prevention Therapy

The treatment strategies across the low-risk groups are shown in (Table 2). OAC use differed significantly across all groups, with increasing use of any oral anticoagulant in parallel with increasing CHA_2DS_2VASc risk score (Figure 2). Even among patients with a $CHA_2DS_2VASc=0$, OAC use was used in almost two thirds of patients. Aspirin use was significantly different at baseline, with the highest use in patients with $CHA_2DS_2VASc=0$ (40.9%), compared with $CHA_2DS_2VASc=1$ (37.6%), females with a $CHA_2DS_2VASc=2$ (32.7%), and patients with a CHA_2DS_2VASc score ≥ 2 (38.6%), ($P=0.01$). The use of antiplatelet therapy with a $P2Y_{12}$ inhibitor, either as single therapy or combined with aspirin, was significantly higher in patients with a CHA_2DS_2VASc score ≥ 2. Apixaban use was significantly higher in females with a $CHA_2DS_2VASc=2$, compared with patients with $CHA_2DS_2VASc=0,1$ and ≥ 2, respectively (16.4% vs. 10.5% vs. 12.0% vs. 13.4%, $P<0.0001$); dabigatran and rivaroxban use were not significantly different across low-risk groups. Patients with a $CHA_2DS_2VASc=0$ were more likely to not be treated with any antithrombotic therapy, although the percentage of patients not treated with any antithrombotic therapy decreased with increasing CHA_2DS_2VASc score.

Outcomes

Event rates and adjusted analyses in the combined cohort are shown in Table 3. Thromboembolic event rates (TIA, stroke, or systemic embolism) were zero per 100 patient-years for $CHA_2DS_2VASc=0$, 0.8 per 100 patient-years in CHA_2DS_2-VASc=1, 0.8 per 100 patient-years in females with a CHA_2DS_2VASc score=2, and 1.7 per 100 patient-years in the $CHA_2DS_2VASc \geq 2$ group ($P=0.17$). All-cause mortality was low among low-risk CHA_2DS_2VASc groups but highest among patients with a $CHA_2DS_2VASc \geq 2$ (5.7 per 100 patient-years) ($P=0.45$). In addition, females with a CHA_2DS_2VASc score=2

Table 1. Baseline Characteristics Across CHA_2DS_2VASc Groups

	$CHA_2DS_2VASc=0$ (N=541)	$CHA_2DS_2VASc=1$ (N=1589)	Females With an Additional Risk Factor (N=670)	$CHA_2DS_2VASc\geq2$ (N=15 598)	*P* Value
Age, y	55 (48–60)	60 (53–63)	63 (59–68)	75 (68–82)	<0.0001
Male	100	84	0	56	<0.0001
Race					
White	88	88	88	88	0.04
Black	4.4	4.5	4.5	4.9	
Hispanic	4.8	4.1	5.4	4.8	
Medical history					
Hypertension	0	54	51	89	<0.0001
Current smoker	18	24	19	22	<0.0001
Cancer	8.0	11	13	24	<0.0001
Coronary artery disease	0	3.0	3.0	37	<0.0001
COPD	3.1	5.0	7.3	15	<0.0001
Obstructive sleep apnea	20	21	15	18	0.004
Significant valvular disease	5.2	9.0	12	22	<0.0001
Heart failure (class III/IV)	0	1.1	1.2	6.4	<0.0001
Diabetes mellitus	0	3.0	4.0	33	<0.0001
BMI, kg/m^2	29 (26–33)	31 (27–36)	31 (26–37)	29 (25–34)	<0.0001
Systolic blood pressure	120 (111–128)	123 (114–134)	125 (116–138)	127 (118–139)	<0.0001
Diastolic blood pressure	78 (70–82)	78 (70–83)	76 (70–82)	72 (66–80)	<0.0001
Serum creatinine, mg/dL	1.0 (0.9–1.1)	1.0 (0.8–1.1)	0.8 (0.7–0.9)	1.0 (0.9–1.3)	<0.0001
LVEF (Normal)	81	76	83	70	<0.0001
AF type					
First detected	36	33	33	25	<0.0001
Paroxysmal	46	44	52	42	
Persistent	14	16	11	14	
Permanent	4.0	7.3	5.0	19	
EHRA score					
No symptoms	29	32	27	37	<0.0001
Mild	50	47	50	45	
Severe	20	19	20	17	
Disabling	2.0	3.0	3.0	2.0	
AF management strategy					
Rate control	46	55	57	67	<0.0001
Rhythm control	54	45	43	33	
Prior cardioversions	36	33	25	26	<0.0001
Prior AAD	39	39	35	36	<0.0001
Catheter ablation of AF	17	10	9.0	4.4	<0.0001
AV node ablation	0.2	1.0	1.3	1.5	0.002
ATRIA score	0	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	3.0 (1.0, 4.0)	<0.0001

Values presented as percentages or median (interquartile range). AAD indicates antiarrhythmic drug; AF, atrial fibrillation; ATRIA, anticoagulation and risk factors in atrial fibrillation; AV, atrioventricular; BMI, body mass index; BPM, beats per minute; CHA_2DS_2VASc, Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke, Vascular Disease, Age (65–74 years), Sex; COPD, chronic obstructive pulmonary disease; creatinine clearance (mg/min per 1.73 m^2) calculated by Cockcroft-Gault formula; EHRA, European Heart Rhythm Association; LVEF, left ventricular ejection fraction.

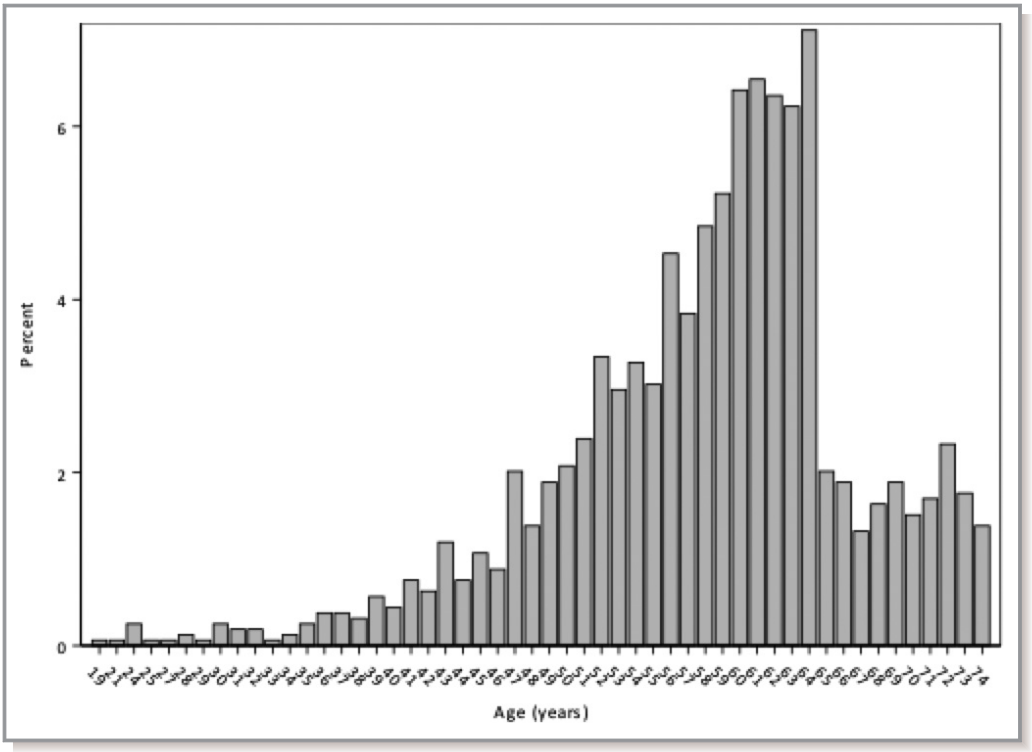

Figure 1. Age distribution among patients with a CHA_2DS_2-VASc score of 1.

had the highest rates of all-cause mortality, cardiovascular death, first major bleeding, first bleeding hospitalization, and first all-cause hospitalization among low-risk CHA_2DS_2VASc groups. Event rates stratified by the use of OAC versus no antithrombotic therapy are shown in (Table 4). For patients with a CHA_2DS_2VASc score of 0,1, and females with a CHA_2DS_2VASc=2, event rates for stroke/TIA/thromboembolism were ≤1.5 events per 100 patient-years, with or without OAC. All-cause mortality for the lowest-risk groups was low and comparable for patients with or without OAC use. For patients with a CHA_2DS_2VASc ≥2, OAC use demonstrated a lower event rate with respect to thromboembolic event rates. A similar trend was noted with respect to all-cause mortality.

CHA_2DS_2VASc=1

The supplemental materials show the characteristics and outcomes for CHA_2DS_2VASc=1 patients. Hypertension was the most common risk factor (N=855/1589 patients, 53.8%) in the combined ORBIT-AF cohort (Table S1). Among CHA_2DS_2VASc=1 patients, females (N=253/1589) were more likely to not be treated with an antiplatelet or OAC (15% vs. 6.0%, P<0.0001), more likely to be treated with aspirin at baseline (49% vs. 36%, P<0.0001), and less likely to be treated with any OAC (49% vs. 74%, P<0.0001) compared with males (Table S2). Thromboembolic event rates (TIA, stroke, or systemic embolism) among men and women were <1 event per 100 patient-years: 0.8 per 100 patient-years for CHA_2DS_2VASc=1, and 0.8 per 100 patient-years for both sexes. All-cause mortality was low among both males (1.0 per 100 patient-years) and females (0). Major adverse cardiovascular and neurologic events were highest in females with a CHA_2DS_2VASc=1 (18.0 vs. 16.0 per 100 patient-years) (Table S3). Stratifying outcomes by the use of OAC versus no antithrombotic therapy demonstrated lower all-cause mortality with OAC treatment (0.8 vs. 1.3 events per 100 patient-years). Stroke rates were <1 event per 100 patient-years irrespective of treatment with OAC (Table 4). Major outcomes for age 65 to 75 years CHA_2DS_2VASc=1 patients in the combined ORBIT-AF and ORBIT-AF II cohorts are shown in Table S4.

Patients With New-Onset AF

A sensitivity analysis was performed in patients with new-onset AF only, in order to ascertain whether incident or prevalent AF altered treatment patterns with respect to stroke prevention and overall outcomes. Patients with new-onset AF accounted for 26% (N=4783/18 398) of patients in the overall cohort. Overall, CHA_2DS_2VASc 0-1 or females with a CHA_2DS_2VASc score=2 accounted for 19.8% (N=936/4738) of all patients with new-onset AF. Any OAC use among patients with low-risk new-onset AF demonstrated a similar

Table 2. Antiplatelet and Anticoagulant Treatment Across CHA_2DS_2VASc Groups

	$CHA_2DS_2VASc=0$ (N=541)	$CHA_2DS_2VASc=1$ (N=1589)	Females With an Additional Risk Factor (N=670)	$CHA_2DS_2VASc\geq2$ (N=15 598)	*P* Value
No antiplatelet or AC	51 (9.4%)	114 (7.2%)	49 (7.3%)	577 (3.7%)	<0.0001
Aspirin at baseline	221 (40.9%)	598 (37.6%)	219 (32.7%)	6021 (38.6%)	0.01
Aspirin and $P2Y_{12}$ at baseline	1 (0.2%)	13 (0.8%)	1 (0.1%)	597 (3.8%)	<0.0001
$P2Y_{12}$ at baseline	2 (0.4%)	21 (1.3%)	5 (0.7%)	1063 (6.8%)	<0.0001
Any oral anticoagulant	326 (60.3%)	1111 (69.9%)	485 (72.4%)	13 137 (84.2%)	<0.0001
Current warfarin use	105 (19.4%)	438 (27.6%)	172 (25.7%)	7585 (48.6%)	<0.0001
Dabigatran at baseline	32 (5.9%)	106 (6.7%)	36 (5.4%)	785 (5.0%)	0.04
Rivaroxaban at baseline	132 (24.4%)	377 (23.7%)	167 (24.9%)	2702 (17.3%)	0.50
Apixaban at baseline	57 (10.5%)	190 (12.0%)	110 (16.4%)	2087 (13.4%)	<0.0001
Aspirin and AC at baseline	58 (10.7%)	238 (15.0%)	86 (12.8%)	4276 (27.4%)	<0.0001
$P2Y_{12}$ and AC at baseline	0 (0.0%)	5 (0.3%)	1 (0.1%)	624 (4.0%)	<0.0001

AC indicates oral anticoagulants including: warfarin, dabigatran, rivaroxaban, and apixaban; CHA_2DS_2VASc, Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke, Vascular Disease, Age (65–74 years), Sex; $P2Y_{12}$; includes clopidogrel, prasugrel, and ticagrelor.

trend compared with the overall analysis, with increasing OAC use paralleling increasing CHA_2DS_2VASc score (Table S5).

Similar to the overall cohort, in patients with new-onset AF, thromboembolic event rates (TIA, stroke, or systemic embolism) increased with CHA_2DS_2VASc scores: zero per 100 patient-years for $CHA_2DS_2VASc=0$, 0.7 per 100 patient-years in $CHA_2DS_2VASc=1$, 1.2 per 100 patient-years in females with a CHA_2DS_2VASc score=2, and 1.6 per 100 patient-years for patients with a $CHA_2DS_2VASc\geq2$. All-cause mortality was low among low-risk CHA_2DS_2VASc groups but highest among patients with a $CHA_2DS_2VASc\geq2$ (4.6 per 100 patient-years) (Table S6). Event rates stratified by the use of OAC versus no antithrombotic therapy in patients with new-onset AF are shown in Table S7. Rates of thromboembolism were low among all low-risk groups irrespective of OAC use, except for females with a $CHA_2DS_2VASc=2$ treated with OAC with an event rate of 2.2 per 100 patient-years.

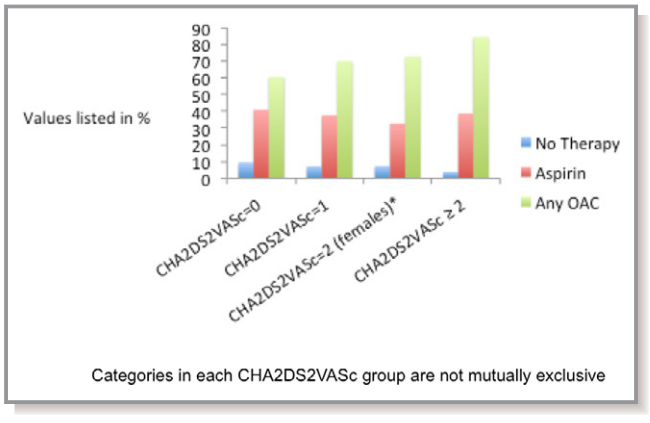

Figure 2. Antiplatelet and antithrombotic treatment strategies in the combined ORBIT AF and ORBIT AF II cohorts. OAC indicates oral anticoagulant.

Discussion

Prevention of thromboembolism is of paramount importance in the care of patients with AF. However, the optimal treatment strategy for patients with AF and a low-risk thromboembolism is unknown. This analysis of low-risk patients in nationwide clinical practice yields several important findings. First, many patients at low risk for embolic events as defined by the CHA_2DS_2VASc score were on systemic OAC. Second, aspirin use was very high in low-risk groups, even in those already treated with OACs at baseline. Third, outcomes were worse with increasing risk as reflected by the CHA_2DS_2VASc score. However, the risk of thromboembolism did not materially differ between patients with $CHA_2DS_2VASc=1$ and females with a CHA_2DS_2VASc score=2. In addition, several notable outliers were noted including the following: a relatively high rate of hospitalizations was documented in low-risk patients, higher risk of stroke/TIA, and the composite outcome (cardiovascular death, stroke/TIA, myocardial infarction, and cardiovascular hospitalization) among females with an additional stroke risk factor taking OAC versus no OAC.

Finally, systemic OAC was associated with lower rates of all-cause mortality, cardiovascular death, and first stroke/TIA among patients with a CHA_2DS_2VASc score ≥2.

Currently, the AHA/ACC/HRS guidelines for the management of AF recommend a risk-based assessment for stroke prevention therapy. For patients with a $CHA_2DS_2VASc=1$, guideline recommendations are equivocal stating that no

Table 3. Adjusted Rates of Major Outcomes Across CHA_2DS_2VASc Groups

Outcome	$CHA_2DS_2VASc=0$*	$CHA_2DS_2VASc=1$*	Female With Additional Risk Factor*	$CHA_2DS_2VASc\geq2$*	*P* Value
All-cause death	2 (0.2) [0.1–1.0]	24 (1.0) [0.7–1.4]	14 (1.4) [1.0–2.3]	1556 (5.7) [5.4–6.0]	0.45
Cardiovascular death	1 (0.1) [0.02–0.9]	5 (0.2) [0.1–0.5]	3 (0.3) [0.1–1.0]	634 (2.3) [2.2–2.5]	0.67
First new-onset-HF diagnosis	6 (0.8) [0.3–1.7]	15 (0.6) [0.4–1.0]	6 (0.6) [0.3–1.3]	515 (1.9) [1.8–2.1]	0.38
First stroke/TIA/systemic embolism	0 (0.0)	19 (0.8) [0.5–1.2]	8 (0.8) [0.4–1.6]	459 (1.7) [1.6–1.9]	0.17
First major bleeding	11 (1.4) [0.8–2.5]	23 (0.9) [0.6–1.4]	24 (2.4) [1.6–3.6]	1081 (4.1) [3.9–4.4]	0.02
First hospitalization (all cause)	168 (26.2) [23.0–30.5]	470 (24.0) [22.0–26.3]	230 (29.4) [25.8–33.4]	7306 (38.7) [37.8–40.0]	0.23
First bleeding hospitalization	5 (0.6) [0.3–1.5]	21 (0.9) [0.6–1.3]	15 (1.5) [0.9–2.5]	937 (3.6) [3.3–3.8]	0.28
First cardiovascular hospitalization	126 (18.5) [15.6–22.0]	345 (16.6) [15.0–18.5]	144 (16.5) [14.0–19.4]	4245 (18.8) [18.3–19.4]	0.03
First noncardio/nonbleed hospitalization	20 (5.1) [3.8–7.0]	144 (6.2) [5.2–7.3]	93 (10.0) [8.1–12.2]	3897 (16.9) [16.4–17.4]	0.001
First cardiovascular death/stroke/TIA/MI/cardiovascular Hospitalization	127 (18.63) [15.7–22.2]	351 (16.94) [15.3–19.0]	146 (16.82) [14.3–19.8]	4418 (19.7) [19.1–20.3]	0.03

CHA_2DS_2VASc indicates Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke, Vascular Disease, Age (65–74 years), Sex; HF, heart failure; MI, myocardial infarction; TIA, transient ischemic attack.
*event # (event # per 100 patient-years) [95% confidence interval].

therapy, ASA alone, or OAC are all reasonable options (Class IIB; Level of Evidence C).[10] In addition, there are few data on the risk of stroke/systemic embolism in females with a $CHA_2DS_2VASc=2$ and few descriptions of contemporary treatment patterns in US clinical practice. Notably, international estimates of risk in this important subgroup have been variable, often with marked differences in absolute risk.[17,18]

Prior studies using the CHA_2DS_2VASc stratification tool have produced differing conclusions regarding the role of OAC in patients with an additional risk factor for stroke/systemic embolism.[19] Lip and colleagues in a large Danish cohort of patients with AF demonstrated that in untreated patients with 1 additional stroke risk factor ($CHA_2DS_2VASc=1$ [male],=2 [female]), strokes rates increased 3-fold compared with untreated low-risk patients ($CHA_2DS_2VASc=0$ [male], =1 [female]).[20] Similarly, Chao and colleagues in a large Taiwanese cohort of patients with AF demonstrated that untreated patients with 1 additional risk factor for stroke derived a benefit from OAC given their increased risk of ischemic stroke.[21] Conversely, Friberg and colleagues, in a large Swedish cohort, showed that untreated patients with 1 additional stroke risk factor had lower risk of ischemic stroke than previously reported and that the use of OAC in this group provided no associated benefit.[18]

Our study is derived from 2 large cohorts of patients with AF from the United States, many of whom were treated with OAC. In comparison to the results from many of the European registries, our data among patients with both new-onset AF and prevalent AF suggest that there is a very low risk of thromboembolic events (stroke/TIA/systemic embolism) among patients with an additional risk factor for stroke. Some of the low event rates may be attributed to the moderate use of OAC with warfarin or direct OACs at baseline, including among patients with a $CHA_2DS_2VASc=0$. However, there were no major differences in event rates in those low-risk patients who were and were not receiving OAC. The fact that up to 40% of the lowest risk patients with a $CHA_2DS_2VASc=0$ were on antiplatelet therapy with aspirin and >60% of all low-risk patients were on OAC underscores several important points: (1) improved implementation of evidence-based guidelines regarding risk stratification for stroke and OAC administration is needed among low-risk patients as our results are in discord with the current AHA/ACC guideline recommendations for stroke prevention in patients with AF with the lowest risk for stroke; (2) the presence of AF and not the overall thromboembolic risk profile may be a primary driver of the administration of therapy for stroke prevention; and (3) practice patterns vary significantly among US physicians, reflecting the poor adherence and lack of consistent application to the guidelines. It is important to note that many low-risk patients, who are younger and more likely to have symptomatic AF, have a class I recommendation for OAC surrounding cardioversion or ablation procedures, which may explain the increased use of OAC. In addition, the relatively high rate of hospitalization in patients at low risk for stroke suggests that these patients have substantial morbidity and a mortality rate that is low but not negligible. While our results are in alignment with recommendations from the AHA/ACC/HRS guidelines for the management of AF for patients with 1 additional stroke risk factor, the European guidelines favor treatment in patients with 1 nonsex risk factor.[12]

Table 4. Unadjusted Major Outcomes Across CHA_2DS_2VASc Groups Stratified by OAC Use

Outcome	$CHA_2DS_2VASc=0$*			$CHA_2DS_2VASc=1$*			Female With Additional Risk Factor*			$CHA_2DS_2VASc\geq2$*		
	No Therapy (N=46)	OAC (N=224)	*P* Value	No Therapy (N=97)	OAC (N=700)	*P* Value	No Therapy (N=48)	OAC (N=321)	*P* Value	No Therapy (N=521)	OAC (N=7247)	*P* Value
All-cause death	1 (1.2)	1 (0.3)	0.30	2 (1.3)	9 (0.8)	0.42	1 (1.2)	4 (0.8)	0.52	89 (9.6)	665 (5.2)	<0.0001
Cardiovascular death	0 (0.0)	1 (0.3)	0.90	0 (0.0)	3 (0.3)	1.00	0 (0.0)	1 (0.2)	0.73	33 (3.6)	260 (2.0)	0.002
First new-onset-HF diagnosis	0 (0.0)	5 (1.6)	0.60	1 (0.6)	7 (0.7)	0.73	0 (0.0)	2 (0.4)	1.00	22 (2.4)	232 (1.8)	0.17
First stroke/TIA/systemic embolism	0 (0.0)	0 (0.0)	–	1 (0.6)	9 (0.8)	0.94	0 (0.0)	7 (1.5)	0.60	15 (1.6)	189 (1.5)	0.63
First major bleeding	2 (2.4)	5 (1.6)	0.50	0 (0.0)	8 (0.8)	0.56	4 (5.2)	9 (2.0)	0.06	44 (5.0)	446 (3.6)	0.03
First hospitalization (all cause)	10 (13.0)	76 (31.4)	0.03	28 (21.5)	214 (25.7)	0.56	18 (31.0)	110 (31.0)	0.91	244 (36.6)	3252 (35.4)	0.53
First bleeding hospitalization	1 (1.2)	3 (1.0)	0.53	0 (0.0)	9 (0.8)	0.50	3 (3.9)	6 (1.3)	0.10	33 (3.7)	400 (3.2)	0.42
First cardiovascular hospitalization	4 (5.1)	55 (21.1)	0.02	18 (13.1)	153 (17.1)	0.44	8 (11.3)	73 (18.3)	0.30	132 (16.7)	1820 (16.7)	0.93
First noncardio/nonbleed Hospitalization	5 (6.3)	17 (5.5)	0.84	13 (8.7)	67 (6.7)	0.30	9 (13.0)	46 (11.0)	0.46	144 (18.3)	1769 (16.1)	0.13
First cardiovascular death/stroke/ TIA/MI/cardiovascular hospitalization	4 (5.1)	55 (21.1)	0.02	18 (13.2)	156 (17.5)	0.40	8 (11.3)	75 (19.0)	0.26	134 (17.0)	1902 (17.6)	0.78

CHA_2DS_2VASc indicates Congestive Heart Failure, Hypertension, Age, Diabetes Mellitus, Stroke, Vascular Disease, Age (65–74 years), Sex; HF, heart failure; MI, myocardial infarction; OAC, oral anticoagulation; TIA, transient ischemic attack.
*event # (event # per 100 patient-years).

The impact of sex on major outcomes in the ORBIT-AF and ORBIT-AF II registries suggest that females have an overall increased risk profile with respect to hospitalizations, bleeding, and mortality. Although the cause of the differential risk is unclear, our findings suggest that female patients with an additional risk factor for stroke have higher risk of adverse events. Future studies are needed to clarify the impact of sex in low-risk CHA_2DS_2VASc populations. Moreoever, disease-modifying therapy, potentially with angiotensin-converting enzyme inhibition or other renin–angiotensin–aldosterone system antagonism, may also provide benefit over the long-term in women with additional risk factors for stroke given their increased risk of incident heart failure. This hypothesis should be tested in a clinical trial.

Limitations

Several limitations need to be acknowledged when considering these data. First, both the ORBIT-AF and ORBIT-AF II study populations were derived from practices participating in a voluntary US registry and may not be representative of all patients with AF in general. Second, the overall low event rate with respect to major outcomes precludes multivariate adjustment in this analysis. Because of the higher incidence of non-CHA_2DS_2VASc risk factors for death such as cancer and chronic obstructive pulmonary disease, we cannot conclude that the risk factors in the CHA_2DS_2VASc risk score are solely responsible for the higher rates of hospitalization and death. In addition, the absolute risk of major outcomes without treatment with antiplatelet or anticoagulants at baseline could not be determined. Many of our low-risk patients had a very high rate of OAC use, which may have confounded our result of no differences in stroke/systemic embolism $CHA_2DS_2VASc=1$ and females with a CHA_2DS_2-VASc score. Additionally, selection bias may have led to selection of sites and patients, which were more likely to be on OAC. Finally, our rates of ischemic events, including stroke, were a combined end point including both TIA and systemic embolism. Several large retrospective registries have suggested that a more “diverse” end point can lead to an overestimation of risk, leading to higher rates of treatment with OAC and potentially increased risk versus benefit.

Conclusions

Although the absolute risk of death and stroke/TIA are low among $CHA_2DS_2VASc=0$-1 and females with a CHA_2DS_2-VASc=2, females with 1 additional risk factor have higher risk of major cardiovascular outcomes and all-cause mortality among low-risk CHA_2DS_2VASc groups. Despite the absence of a Class I recommendation according to the AHA/ACC/HRS

AF guidelines,[22] in contemporary US clinical practice, 60% to 72% of low-risk patients with AF receive OAC. Randomized trials are needed to clarify the optimal anticoagulation strategy in patients with $CHA_2DS_2VASc=0$, 1 or women with 1 additional risk factor.

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SUPPLEMENTAL MATERIAL

Data S1. ORBIT-AF II Investigators

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Table S1. Tabulation of Components of CHA_2DS_2VASc risk score in patients with a $CHA_2DS_2VASc=1$ in the combined ORBIT-AF and ORBIT-AF II cohort.

CHF	HTN	Age (>75)	DM	CVA/TIA	Vascular Disease	Age (65-74)	Sex (Female)
109 (6.9%)	855 (53.8%)	--	39 (2.5%)	--	56 (3.5%)	277 (17.4%)	253 (15.9%)

CHF: Congestive Heart Failure; CVA: Cerebrovascular Accident; DM: Diabetes Mellitus; HTN: Hypertension; Vascular Disease= Coronary Artery Disease or Aortic Plaque or Peripheral Vascular Disease

Table S2. Antiplatelet and Antithrombotic treatment stratified by gender for $CHA_2DS_2VASc=1$ patients in the combined ORBIT-AF and ORBIT-AF II cohort.

	Male (N=1336)	Female (N=253)	Overall (N=1589)	P Value
No antiplatelet or AC	77 (6.0%)	37 (15%)	114 (7.0%)	<. 0001
Aspirin at baseline	475 (36%)	123 (49%)	598 (37%)	<. 0001
Aspirin and $P2Y_{12}$ at baseline	13 (1.0%)	0 (0.0%)	13 (1.0%)	.12
$P2Y_{12}$ at baseline	21 (2.0%)	0 (0.0%)	21 (1.0%)	.04
Any Oral Anticoagulant	988 (74%)	123 (49%)	1111 (70%)	<. 0001
Current Warfarin Use	401 (30%)	37 (15%)	438 (27%)	<. 0001
Dabigatran at baseline	94 (7%)	12 (5%)	106 (7%)	.20
Rivaroxaban at baseline	332 (25%)	45 (18%)	377 (24%)	.0003
Apixaban at baseline	161 (12%)	29 (12%)	190 (12%)	.40
Aspirin and AC at baseline	208 (16%)	30 (12%)	238 (15%)	.13
$P2Y_{12}$ and AC at baseline	5 (0.4%)	0 (0.0%)	5.0 (0.3%)	.33

AC; oral anticoagulants including: warfarin, dabigatran, rivaroxaban, and apixaban; $P2Y_{12}$; includes clopidogrel, prasugrel, and ticagrelor

Table S3. Major Outcomes stratified by gender for $CHA_2DS_2VASc=1$ patients in the combined ORBIT-AF and ORBIT-AF II cohort.

Outcome	Male* (N=1336)	Female* (N=253)	Overall*
All-cause Death	24 (1.0)[0.8-1.7]	0 (0.0)	24 (1.0)[0.7-1.4]
Cardiovascular Death	5 (0.2)[0.1-0.6]	0 (0.0)	5 (0.2)[0.1-0.5]
1st New-Onset-HF Diagnosis	13 (0.6)[0.4-1.1]	2 (0.5)[0.1-2.1]	15 (0.6)[0.4-1.0]
1st Stroke/TIA/systemic embolism	16 (0.8)[0.5-1.3]	3 (0.8)[0.3-2.5]	19 (0.8)[0.5-1.2]
1st Major Bleeding	20 (1.0)[0.6-1.5]	3 (0.8)[0.3-2.5]	23 (0.9)[0.6-1.4]
1st Hospitalization (All cause)	395 (23.7)[21.5-26.2]	75 (25.6)[21.0-32.3]	470 (24.0)[22.0-26.3]
1st Bleeding Hospitalization	17 (0.8)[0.5-1.3]	4 (1.1)[0.4-2.9]	21 (0.9)[0.6-1.3]
1st Cardiovascular Hospitalization	290 (16.4)[14.6-18.4]	55 (17.6)[13.5-22.9]	345 (16.6)[15.0-18.4]
1st Non-cardio/Non-bleed Hospitalization	121 (6.1)[5.1-7.3]	23 (6.6)[4.4-9.9]	144 (6.2)[5.2-7.3]
Major Adverse Cardiovascular/Neurologic Events	295 (16.7)[15.0-18.8]	56 (18.0)[13.9-23.4]	351 (16.9)[15.3-19.0]

CV: Cardiovascular; HF: Heart Failure; MI: Myocardial Infarction TIA: Transient Ischemic Data; *event # (event # per 100 patient-years)[95% Confidence Intervals]; Major Adverse Cardiovascular/Neurologic Events (MACNE): Composite of CV death/Stroke/TIA/MI/CV Hospitalization

Table S4. Major Outcomes for age 65-75 $CHA_2DS_2VASc=1$ patients in the combined ORBIT-AF and ORBIT-AF II cohorts

Outcome	Age 65-75
All-cause Death	8 (1.8) [0.9-3.6]
Cardiovascular Death	1 (0.2) [0.0-1.6]
1st New-Onset-HF Diagnosis	2 (0.5) [0.1-1.8]
1st Stroke/TIA/systemic embolism	4 (0.9) [0.3-2.4]
1st Major Bleeding	4 (0.9) [0.3-2.4]
1st Hospitalization (All cause)	82 (23.0) [18.5-28.6]
1st Bleeding Hospitalization	4 (0.9) [0.3-2.4]
1st Cardiovascular Hospitalization	55 (14.3) [11.0-18.7]
1st Non-cardio/Non-bleed Hospitalization	29 (6.9) [4.8-9.9]
Major Adverse Cardiovascular/Neurologic Events	56 (14.6) [11.2-19.0]

CV: Cardiovascular; HF: Heart Failure; MI: Myocardial Infarction TIA: Transient Ischemic Data; *event # (event # per 100 patient-years)[95% Confidence Intervals]; Major Adverse Cardiovascular/Neurologic Events (MACNE): Composite of CV death/Stroke/TIA/MI/CV Hospitalization

Table S5. Antiplatelet and Anticoagulant treatment amongst low risk CHA_2DS_2VASc groups among New Onset AF Patients

	$CHA_2DS_2VASc=0$ (N=195)	$CHA_2DS_2VASc=1$ (N=521)	Females with an additional risk factor (N=220)	$CHA_2DS_2VASc\geq2$ (N= 3847)	P Value
No antiplatelet or AC	17 (8.7%)	51 (9.8%)	15 (6.8%)	157 (4.1%)	<.0001
Aspirin at baseline	84 (43.1%)	179 (34.4%)	67 (30.5%)	1345 (35.0%)	.05
Aspirin and $P2Y_{12}$ at baseline	1 (0.5%)	4 (0.8%)	0 (0.0%)	135 (3.5%)	<.0001
$P2Y_{12}$ at baseline	1 (0.5%)	7 (1.3%)	0 (0.0%)	247 (6.4%)	<.0001
Any Oral Anticoagulant	112 (57.4%)	349 (67.0%)	164 (74.5%)	3281 (85.3%)	<.0001
Current Warfarin Use	21 (10.8%)	80 (15.4%)	38 (17.3%)	1078 (28.0%)	<.0001
Dabigatran at baseline	9 (4.6%)	37 (7.1%)	12 (5.5%)	228 (5.9%)	.60`
Rivaroxaban at baseline	59 (30.3%)	170 (32.6%)	78 (35.5%)	1149 (29.9%)	.20
Apixaban at baseline	23 (11.8%)	62 (11.9%)	36 (16.4%)	827 (21.5%)	<.0001
Aspirin and AC at baseline	18 (9.2%)	59 (11.3%)	26 (11.8%)	966 (25.1%)	<.0001
$P2Y_{12}$ and AC at baseline	0 (0.0%)	3 (0.6%)	0 (0.0%)	159 (4.1%)	<.0001

AC; oral anticoagulants including: warfarin, dabigatran, rivaroxaban, and apixaban; CHA_2DS_2VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, Age (65-74), **S**ex; $P2Y_{12}$; includes clopidogrel, prasugrel, and ticagrelor

Table S6. Major Outcomes by CHA_2DS_2VASc group in the combined ORBIT-AF and ORBIT-AF II cohorts among New Onset AF Patients

Outcome	$CHA_2DS_2VASc=0$*	$CHA_2DS_2VASc=1$*	Female with additional risk factor*	$CHA_2DS_2VASc\geq2$*
All-cause Death	1 (0.5) [0.1-3.2]	8 (1.3) [0.7-2.7]	2 (0.8) [0.2-3.2]	179 (4.6) [4.0-5.3]
Cardiovascular Death	0 (0.0)	2 (0.3) [0.1-1.3]	2 (0.8) [0.2-3.2]	70 (1.8) [1.4-2.3]
1st New-Onset-HF Diagnosis	2 (0.9) [0.2-3.6]	3 (0.5) [0.2-1.6]	1 (0.4) [0.1-2.9]	77 (2.0) [1.6-2.5]
1st Stroke/TIA/systemic embolism	0 (0.0)	4 (0.7) [0.3-1.8]	3 (1.2) [0.4-3.8]	62 (1.6) [1.3-2.1]
1st Major Bleeding	7 (3.2) [1.5-6.8]	5 (0.8) [0.4-2.0]	2 (0.8) [0.2-3.2]	131 (3.5) [2.9-4.1]
1st Hospitalization (All cause)	51 (27.2) [20.7-35.8]	133 (27.2) [23.0-32.2]	72 (38.3) [30.4-48.2]	1291 (44.3) [41.8-46.6]
1st Bleeding Hospitalization	3 (1.4) [0.4-4.2]	4 (0.7) [0.3-1.8]	2 (0.8) [0.2-3.2]	127 (3.4) [2.8-4.0]
1st Cardiovascular Hospitalization	34 (17.1) [12.2-24.0]	93 (17.8) [14.6-21.9]	47 (22.7) [17.0-30.1]	741 (22.3) [20.6-23.8]
1st Non-cardio/Non-bleed Hospitalization	13 (6.1) [3.5-10.5]	38 (6.7) [4.9-9.2]	24 (10.3) [6.9-15.4]	478 (13.4) [12.2-14.6]
Major Adverse Cardiovascular/Neurologic Events	34 (17.1) [12.2-24.0]	94 (18.1) [14.8-22.1]	48 (23.5) [17.7-31.1[	767 (23.1) [21.5-24.7]

CHA_2DS_2VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, Age (65-74), **S**ex; CV: Cardiovascular; HF, Heart Failure; MI: Myocardial Infarction; TIA, Transient Ischemic Data; *event # (event # per 100 patient-years) [95% Confidence Interval]; Major Adverse Cardiovascular/Neurologic Events (MACNE): Composite of CV death/Stroke/TIA/MI/CV Hospitalization

Table S7. Major Outcomes across CHA_2DS_2VASc groups for New Onset AF patients stratified by OAC use

Outcome	$CHA_2DS_2VASc=0$*		$CHA_2DS_2VASc=1$*		Female with additional risk factor*		$CHA_2DS_2VASc \geq 2$*	
	No Therapy (N=14)	OAC (N=84)	No Therapy (N=42)	OAC (N=243)	No Therapy (N=15)	OAC (N=119)	No Therapy (N=117)	OAC (N=1590)
All-cause Death	1 (6.5)	0 (0.0)	1 (2.0)	3 (1.0)	0 (0.0)	1 (0.7)	17 (12.0)	80 (4.2)
Cardiovascular Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	6 (4.2)	27 (1.4)
1st New-Onset-HF Diagnosis	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.6)	33 (1.8)
1st Stroke/TIA/systemic embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	3 (2.2)	3 (2.1)	33 (1.8)
1st Major Bleeding	1 (6.5)	3 (3.5)	0 (0.0)	2 (0.7)	0 (0.0)	2 (1.4)	5 (3.5)	54 (2.9)
1st Hospitalization (All cause)	1 (6.5)	28 (39.7)	12 (31.4)	64 (27.6)	4 (43.0)	38 (35.7)	44 (39.1)	569 (39.6)
1st Bleeding Hospitalization	1 (6.5)	1 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1.4)	3 (2.1)	49 (2.6)
1st Cardiovascular Hospitalization	0 (0.0)	18 (23.2)	7 (17.2)	43 (17.3)	2 (18.9)	25 (21.3)	23 (17.7)	318 (19.7)
1st Non-cardio/Non-bleed Hospitalization	0 (0.0)	6 (7.0)	6 (13.6)	16 (5.8)	1 (7.5)	13 (9.8)	18 (14.1)	211 (12.0)
Major Adverse Cardiovascular/Neurologic Events	0 (0.0)	18 (23.2)	7 (17.2)	43 (17.3)	2 (18.9)	26 (22.7)	23 (17.7)	336 (20.9)

CHA_2DS_2VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, Age (65-74), **S**ex; CV: Cardiovascular; HF: Heart Failure; Myocardial Infarction: MI; TIA: Transient Ischemic Data; *event # (event # per 100 patient-years); Major Adverse Cardiovascular/Neurologic Events (MACNE): Composite of CV death/Stroke/TIA/MI/CV Hospitalization

Figure S1. Age Histogram of CHA_2DS_2VASc= 0 patients