Comparison of Patient-Reported Care Satisfaction, Quality of Warfarin Therapy, and Outcomes of Atrial Fibrillation: Findings From the ORBIT-AF Registry

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Background—Patient satisfaction with therapy is an important metric of care quality and has been associated with greater medication persistence. We evaluated the association of patient satisfaction with warfarin therapy to other metrics of anticoagulation care quality and clinical outcomes among patients with atrial fibrillation (AF).

Methods and Results—Using data from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, patients were identified with AF who were taking warfarin and had completed an Anti-Clot Treatment Scale (ACTS) questionnaire, a validated metric of patient-reported burden and benefit of oral anticoagulation. Multivariate regressions were used to determine association of ACTS burden and benefit scores with time in therapeutic international normalized ratio range (TTR; both ≥75% and ≥60%), warfarin discontinuation, and clinical outcomes (death, stroke, major bleed, and all-cause hospitalization). Among 1514 patients with AF on warfarin therapy (75±10 years; 42% women; CHA_2DS_2-VASc 3.9±1.7), those most burdened with warfarin therapy were younger and more likely to be women, have paroxysmal AF, and to be treated with antiarrhythmic drugs. After adjustment for covariates, ACTS burden scores were independent of TTR (TTR ≥75%: odds ratio, 1.01 [95% CI, 0.99−1.03]; TTR ≥60%: odds ratio, 1.01 [95% CI, 0.98−1.05]), warfarin discontinuation (odds ratio, 0.99; 95% CI, 0.97−1.01), or clinical outcomes. ACTS benefit scores were also not associated with TTR, warfarin discontinuation, or clinical outcomes.

Conclusions—In a large registry of patients with AF taking warfarin, ACTS scores provided independent information beyond other traditional metrics of oral anticoagulation care quality and identified patient groups at high risk for dissatisfaction with warfarin therapy. (***J Am Heart Assoc***. 2019;8:e011205. DOI: 10.1161/JAHA.118.011205.)

Key Words: anticoagulation • atrial fibrillation • patient-reported outcome • patient-centered care • warfarin

Patient-centered care has been increasingly recognized as an important aspect of healthcare delivery, incorporated into contemporary healthcare reform efforts,[1] and associated with superior clinical outcomes in certain contexts.[2] Mechanisms for association between patient-centered care and clinical outcomes include higher treatment persistence, which may mediate an association between patient satisfaction and clinical outcomes. For oral anticoagulation (OAC) with warfarin in patients with atrial fibrillation (AF), time in therapeutic international normalized ratio (INR) range (TTR)[3] has been associated with lower risk of thromboembolism and bleeding.[4,5] While there are many contributors to TTR, patient satisfaction with anticoagulation may significantly influence warfarin adherence and persistence. However, to date, there are few data assessing the impact of patient-reported OAC outcomes on clinical outcomes. Additionally, there are

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Clinical Perspective

What Is New?

- Patients reporting the most burden from warfarin therapy, as determined by the Anti-Clot Treatment Scale questionnaire, were younger and more likely to be women, have paroxysmal atrial fibrillation, and be treated with antiarrhythmic drugs.
- Patient quartiles reporting the least burden from warfarin therapy had higher 1-year time in therapeutic international normalized ratio range and less warfarin discontinuation, although there was no association after multivariate adjustment.

What Are the Clinical Implications?

- Anti-Clot Treatment Scale scores provide independent information beyond other traditional metrics of oral anticoagulation care quality.
- With several available alternatives to warfarin therapy, patient-reported care satisfaction with warfarin therapy should be proactively assessed.

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currently several alternatives to warfarin therapy including the non–vitamin K antagonist oral anticoagulants that could be considered for use among individuals with low satisfaction with warfarin therapy. Therefore, understanding the extent of patient satisfaction (or lack thereof) with warfarin therapy and characterization of these groups would be of value.

Using data from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) and the Anti-Clot Treatment Scale (ACTS) questionnaire, the objectives of these analyses were to: (1) describe characteristics of patients with high and low satisfaction with warfarin therapy, and (2) determine whether patient satisfaction with warfarin therapy is associated with TTR, warfarin discontinuation, and clinical outcomes.

Methods

ORBIT-AF is an outpatient-based registry of patients with incident or prevalent AF who were enrolled from June 29, 2010, to August 9, 2011, in the United States. Patients were enrolled from geographically diverse settings and care models (ie, primary care, cardiology, and/or electrophysiology managed patients in academic, private, and/or government healthcare settings) to create a representative sample of patients with AF. An adaptive design was used to ensure a representative cohort by geography and care model. Study initiation and coordination was overseen by the Duke Clinical Research Institute. Methods for registry design and execution have been previously described in detail.[6–8] 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.

Patients who met registry criteria were enrolled consecutively from participating sites. Registry inclusion criterion was electrocardiographic evidence of AF. Exclusion criteria were: (1) age younger than 18 years; (2) AF from a reversible cause (eg, cardiac surgery, thyroid disease); (3) life expectancy <6 months; and (4) inability to provide informed consent or follow-up. A preplanned patient-reported outcomes substudy targeted enrollment of ≈1500 patients. All sites were eligible to participate in the substudy. Registry data collection was primarily derived from patient medical records with outcomes of interest collected at 6-month intervals with central adjudication.

Patients included in the patient-reported outcomes substudy completed the ACTS questionnaire at the time of registry enrollment. The ACTS is a 15-item instrument that is summarized as 2 scales that represent both negative (limitations, inconveniences, burdens) and positive (confidence, reassurance, satisfaction) aspects of anticoagulation treatment: ACTS burdens (12 items), and ACTS benefits (3 items). For each item, patient experience with anticoagulation treatment is rated on a 5-point Likert scale from "Not at all" to "Extremely." The 12 items of ACTS burdens are reverse coded (scored 5 to 1), whereas the 3 items of ACTS benefits are coded normally (scored 1–5), so that higher scores indicate greater patient satisfaction. The first burden question is "During the past 4 weeks how much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in vigorous physical activities (eg, exercise, sports, dancing)?" The first benefit question is "During the past 4 weeks how confident are you that your anti–clot treatment will protect your health (eg, prevent blood clots, stroke, heart attack, deep vein thrombosis, embolism)?" The full questionnaire is available in Table S1. Item scores are summed across domains to give an ACTS Burdens score ranging from 12 to 60 and an ACTS benefits score ranging from 3 to 15. A patient must have data for all items of a scale for the scale to be calculated.

The ACTS was built on the conceptual framework of the Duke Anticoagulation Satisfaction Scale and was developed to assess both warfarin therapy and non–vitamin K antagonist OACs. In validation studies, the ACTS has been shown to consistently satisfy traditional psychometric criteria for questionnaire acceptability, scaling assumptions, reliability, and validity across cultures and languages.[9–11] The ACTS has also been used in the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) clinical trial, which evaluated rivaroxaban versus warfarin therapy.[12]

The primary predictors (independent variables) were the ACTS scores (burden and benefit) in patients treated with

warfarin. The primary outcomes (dependent variables) were TTR between INR 2.0 to 3.0 and warfarin discontinuation over a 1-year period after completing the ACTS questionnaire. We choose TTR ≥75% and ≥60% as thresholds in our analysis, as these represent the desired TTR threshold that maximizes effectiveness and safety and minimum threshold to demonstrate benefit of warfarin over aspirin, respectively.[4,13] TTR was calculated using the modified Rosendaal method of linear interpolation and its calculation in the ORBIT-AF registry has been previously described.[14] Warfarin discontinuation was assessed at 6 and 12 months, ascertained at patient follow-up visits. We also evaluated clinical outcomes of death, ischemic stroke/transient ischemic attack (TIA) or systemic embolism, major bleed,[15] and all-cause hospitalization.

Baseline demographics and clinical characteristics were compared between patient quartiles of ACTS burden and benefit scores. Continuous variables are presented as median (25th–75th percentile) or mean and SD where noted, with differences assessed using the Kruskal–Wallis test. Categorical variables are presented as frequency (percentage) with differences assessed using chi-square test. We determined the Pearson correlation coefficient between patients' ACTS burden and benefit scores.

The frequency (percentage) of TTR ≥75%, TTR ≥60%, and warfarin discontinuation are presented by patient quartiles of ACTS burden and benefit scores. The frequency and incidence rate of clinical outcomes per 100-patient years of follow-up are also presented by quartile.

Logistic regression was used to determine the association between TTR ≥75%, TTR ≥60%, and ACTS scores with generalized estimating equations included to account for site variation. Cox proportional hazards models were used to determine the association between both warfarin discontinuation and clinical outcomes and ACTS scores, with a robust covariance estimate included to account for site variation. ACTS scores were treated as a continuous variable in all regressions. Warfarin discontinuation time was treated as discrete, with follow-up at either 6 or 12 months. We performed sensitivity analyses by stratifying patients into low to moderate and high stroke risk by CHA_2DS_2-VASc score, defined as scores <4 and ≥4, respectively. Both unadjusted and multivariate-adjusted models were performed. Multivariate analysis included covariates, selected based on face validity, for demographics, medical history, AF history, medications, functional status, care model, and region, with the full covariate list provided in Table S2. All continuous covariates were tested for a linear association with each outcome, and any nonlinear relationship was accounted for using linear splines. Missing covariate data were handled by multiple imputation using Markov chain Monte Carlo or regression methods. Final estimates and standard errors reflect the combined analysis over 5 imputed data sets.

The present study and the ORBIT-AF registry were approved by Duke University's institutional review board, and each site received equivalent approval subject to local regulation. All patients provided written, informed consent. The senior author had full access to all study data and takes responsibility for its integrity and the data analysis. All analyses were performed using SAS, version 9.3 (SAS Institute).

Results

The overall ORBIT-AF registry included 10 137 patients of whom 1514 (15%) completed ACTS questionnaires (ACTS burden: 1507 patients; ACTS benefit: 1513 patients), were taking warfarin, and completed follow-up (Figure). As compared with patients from ORBIT-AF taking warfarin who were excluded (5701), included patients (1514) were similar by age and sex, had slightly lower CHA_2DS_2-VASc scores (3.9±1.7 versus 4.1±1.7; $P<0.001$), and were slightly less likely to have nonparoxysmal AF (48.5% versus 51.4%, $P<0.001$) (Table S3).

The analysis cohort of 1514 patients had a mean age of 75±10 years, 42% were women, and a mean CHA_2DS_2-VASc score of 3.9±1.7 (CHA_2DS_2-VASc <4: 581 patients; CHA_2DS_2-VASc ≥4: 933 patients). As highlighted in Table 1, for the ACTS burden score, the patient quartiles reporting more burden from warfarin therapy were younger and more likely to be women, have paroxysmal AF, and be treated with antiarrhythmic drugs. For the ACTS benefit score, baseline characteristics were similar across score quartiles. Mean ACTS burden score was 53.7±7.0 (possible range 12–60) with means of 59.6±0.5 and 43.5±6.4 for the quartiles least and most burdened by warfarin therapy ($P<0.001$), respectively. Mean ACTS benefit score was 10.7±3.4 (possible range 3–15), with means of 14.8±0.4 and 5.2±1.9 for quartiles with the highest and lowest benefit ($P<0.001$), respectively (Table S4). Patients' ACTS burden and benefit scores were weakly correlated ($r=0.12$, $P<0.001$).

Quality of Warfarin Therapy

For the ACTS burden score, patient quartiles reporting less burden from warfarin therapy had higher 1-year rates of TTR (TTR ≥75% quartile 4: 41.5% versus quartile 1: 34.2% [$P=0.017$]; TTR ≥60% quartile 4: 62.0% versus quartile 1: 57.3% [$P=0.035$]), and no significant difference in warfarin discontinuation (quartile 4: 17.8% versus quartile 1: 23.2% [$P=0.096$]) (Table 2). In multivariate analyses, being less burdened by warfarin therapy was not associated with TTR (TTR ≥75%: odds ratio [OR], 1.01; 95% CI, 0.99–1.03 [$P=0.153$]; TTR ≥60%: OR, 1.01; 95% CI, 0.99–1.03 [$P=0.208$]) or warfarin discontinuation (OR, 0.99; 95% CI,
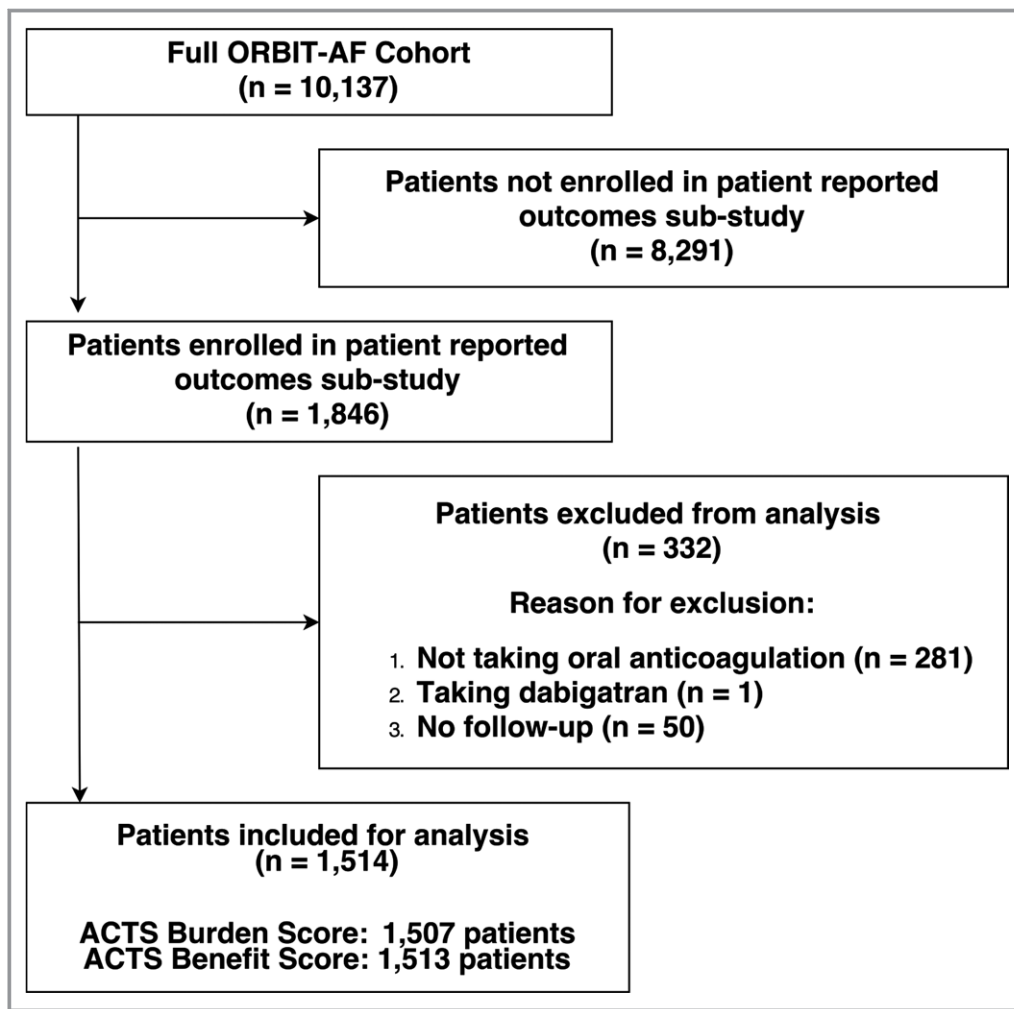
Figure. Inclusion and exclusion criteria used to select analysis cohort. ACTS indicates Anti-Clot Treatment Scale; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

0.97−1.01 [*P*=0.157]) (Table 3). When patients were stratified by CHA_2DS_2-VASc score, univariate association between burden score and TTR ≥75% was limited to patients with CHA_2DS_2-VASc ≥4. However, after multivariate adjustment this association did not reach significance (OR, 1.02; 95% CI, 1.00−1.05 [*P*=0.072]) (Table S5). For the ACTS benefit score, there were no differences across score quartiles for TTR (both ≥75% and ≥60%) and warfarin discontinuation (Table 2). In multivariate analyses, there were no associations between benefit score and TTR or warfarin discontinuation in the full cohort, patients with CHA_2DS_2-VASc <4, or patients with CHA_2DS_2-VASc ≥4 (Table 3) (Tables S5 and S6).

Clinical Outcomes

After a mean follow-up of 27.8±9.6 months, for the ACTS burden score, patient quartiles reporting less burden with warfarin therapy had a higher unadjusted incidence rate of ischemic stroke/transient ischemic attack or systemic

embolism (quartile 4: 1.9 versus quartile 1: 1.0 per 100 patient-years; *P*=0.026) and similar rates of overall mortality (quartile 4: 5.1 versus quartile 1: 4.4 per 100 patient-years; *P*=0.450), major bleeds (quartile 4: 3.1 versus quartile 1: 3.2 per 100 patient-years; *P*=0.893), and all-cause hospitalization (quartile 4: 34.0 versus quartile 1: 37.7 per 100 patient-years; *P*=0.517) (Table 2). In multivariate analyses, patient-reported burden with warfarin therapy was not associated with clinical outcomes in the full cohort, patients with CHA_2DS_2-VASc <4, or patients with CHA_2DS_2-VASc ≥4 (Table 3) (Tables S5 and S6). For the ACTS benefit score, clinical outcomes were similar across score quartiles (Table 2) and, in multivariate analyses, the score was not associated with clinical outcomes in the full cohort (Table 3). For patients with CHA_2DS_2-VASc ≥4, there was a borderline association between benefit score and overall mortality (OR, 0.95; 95% CI, 0.91−1.00 [*P* 0.047]) (Table S5). However, there was no association with benefit score and TTR or warfarin discontinuation to explain how a reduction in mortality would be mediated (Table 3) (Tables S5 and S6).

Table 1. Baseline Characteristics by ACTS Burden Score Quartile

	ACTS Burden Score					
	Total (N=1507)	Quartile 1 (n=371)	Quartile 2 (n=418)	Quartile 3 (n=288)	Quartile 4* (n=430)	P Value[†]
ACTS score, mean±SD	53.7±7.0	43.5±6.4	53.9±1.7	57.5±0.5	59.6±0.5	<0.001
Demographics						
Age, mean±SD	74.5±9.8	72.6±10.5	74.1±9.8	75.1±9.2	76.2±9.2	<0.001
Women	637 (42.3)	167 (45.0)	194 (46.4)	135 (46.9)	141 (32.8)	<0.001
Race						0.499
White	1371 (91.0)	337 (90.8)	381 (91.2)	264 (91.7)	389 (90.5)	
CHADS2 score group						0.059
0 or 1	399 (26.5)	112 (30.2)	109 (26.1)	75 (26.0)	103 (24.0)	
≥2	1108 (73.5)	259 (69.8)	309 (73.9)	213 (74.0)	327 (76.0)	
CHADS$_2$ score	2.3±1.3	2.2±1.3	2.3±1.3	2.3±1.3	2.3±1.2	0.480
CHA$_2$DS$_2$-VASc score	3.9±1.7	3.9±1.8	4.0±1.7	4.0±1.8	3.9±1.5	0.771
Nonparoxysmal AF	729 (48.4)	162 (43.7)	193 (46.2)	133 (46.2)	241 (56.1)	0.015
Heart failure	426 (28.3)	123 (33.2)	119 (28.5)	71 (24.7)	113 (26.3)	0.070
CKD	523 (34.7)	115 (33.7)	161 (41.7)	107 (41.5)	140 (35.8)	0.071
CAD	473 (31.4)	124 (33.4)	131 (31.3)	76 (26.4)	142 (33.0)	0.204
Myocardial infarction	210 (13.9)	51 (13.8)	55 (13.2)	35 (12.2)	69 (16.1)	0.461
Stroke/TIA	251 (16.7)	54 (14.6)	77 (18.4)	56 (19.4)	64 (14.9)	0.195
PAD	183 (12.1)	40 (10.8)	60 (14.4)	35 (12.2)	48 (11.2)	0.400
Diabetes mellitus	414 (27.5)	98 (26.4)	112 (26.8)	77 (26.7)	127 (29.5)	0.729
Hypertension	1262 (83.7)	319 (86.0)	341 (81.6)	237 (82.3)	365 (84.9)	0.300
Anemia	225 (14.9)	54 (14.6)	75 (17.9)	38 (13.2)	58 (13.5)	0.220
Gastrointestinal bleed	100 (6.6)	24 (6.47)	27 (6.46)	20 (6.94)	29 (6.74)	0.993
Care model						
Payor/insurance						<0.001
Medicaid/Medicare	1111 (73.7)	242 (65.2)	316 (75.6)	213 (74.0)	340 (79.1)	
Private	318 (21.1)	109 (29.4)	78 (18.7)	60 (20.8)	71 (16.5)	
Other	78 (5.2)	20 (5.4)	24 (5.7)	15 (5.2)	19 (4.4)	
OAC management						
Home INR monitoring	46 (3.1)	12 (3.2)	14 (3.4)	9 (3.1)	11 (2.6)	0.913
Anticoagulation clinic	598 (39.7)	146 (39.4)	179 (42.8)	112 (38.9)	161 (37.4)	0.437
Cardiology care	1260 (83.6)	320 (86.3)	353 (84.5)	221 (76.7)	366 (85.1)	0.005
Medication use						
Prior warfarin use[‡]	1392 (92.4)	345 (93.0)	379 (90.7)	271 (94.1)	397 (92.3)	0.371
β-Blockers	1012 (67.2)	239 (64.4)	282 (67.5)	193 (67.0)	298 (69.3)	0.568
Calcium channel blockers[§]	249 (16.5)	72 (19.4)	74 (17.7)	35 (12.2)	68 (15.8)	0.076
Digoxin	385 (25.6)	98 (26.4)	104 (24.9)	64 (22.2)	119 (27.7)	0.397
Amiodarone	125 (8.3)	32 (8.6)	49 (11.7)	18 (6.3)	26 (6.1)	0.012
Rhythm control agents	383 (25.4)	111 (29.9)	120 (28.7)	72 (25.0)	80 (18.6)	<0.001
Antiplatelet agents	554 (36.8)	143 (38.5)	152 (36.4)	98 (34.0)	161 (37.4)	0.671
Statins	784 (52.0)	177 (47.7)	213 (51.0)	158 (54.9)	236 (54.9)	0.163

Values are expressed as mean±SD or number (percentage). AF indicates atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; INR, international normalized ratio; OAC, oral anticoagulation; PAD, peripheral artery disease; TIA, transient ischemic attack.
*Anti-Clot Treatment Scale (ACTS) score quartile with least burden.
[†]Differences between quartiles assessed using chi-square test and Kruskal–Wallis test for categorical and continuous variables, respectively.
[‡]Before enrollment in ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation).
[§]Nondihydropyridine calcium channel blockers.

Table 2. Incidence of Warfarin and AF Outcomes by ACTS Quartile

ACTS Benefit Score	Total (N=1513)	Quartile 1 (n=310)	Quartile 2 (n=379)	Quartile 3 (n=492)	Quartile 4* (n=332)	P Value[†]
TTR ≥75%, No. (%)[‡]	503 (40.4)	94 (36.4)	119 (39.1)	174 (42.8)	116 (41.9)	0.184
TTR ≥60%, No. (%)[‡]	753 (62.8)	153 (59.3)	186 (61.2)	269 (66.1)	175 (63.2)	0.100
Warfarin discontinuation, No. (%)[‡]	300 (20.4)	61 (20.5)	76 (20.5)	100 (20.8)	63 (19.4)	0.867
Overall mortality (IR)	160 (4.6)	41 (5.7)	32 (3.7)	55 (4.8)	32 (4.1)	0.357
Cardioembolic event (IR)[§]	44 (1.3)	6 (0.8)	14 (1.6)	16 (1.4)	8 (1.0)	0.847
Major bleed (IR)	106 (3.1)	33 (4.8)	21 (2.5)	31 (2.8)	21 (2.8)	0.115
All-cause hospitalization (IR)	810 (34.2)	176 (37.5)	214 (37.1)	245 (31.0)	175 (32.7)	0.089

AF indicates atrial fibrillation, IR, incidence rate per 100 patient-years of follow-up; TTR, time in therapeutic range.
*Anti-Clot Treatment Scale (ACTS) score quartile with least burden or greatest benefit.
[†]Differences between quartiles assessed using the chi-squared test and Kruskal–Wallis test for categorical and continuous variables, respectively.
[‡]Over 1 year.
[§]Stroke, systemic embolism, transient ischemic attack.

Discussion

In patients with AF taking warfarin in the ORBIT-AF registry, patients most burdened by warfarin therapy were younger and more likely to be women, have paroxysmal AF, and be treated with antiarrhythmic drugs. ACTS burden and benefit scores were not associated with INR control, medication persistence, or clinical outcomes, suggesting that ACTS scores provide independent information beyond other traditional metrics of anticoagulation care quality.

Subjective burden of OAC is variable, influenced by patient values, preferences, and OAC strategy.[16–18] Recognition of patient groups at high risk for dissatisfaction with warfarin therapy has the potential to improve quality-adjusted life

Table 3. Association of ACTS Scores With Warfarin and AF Outcomes

	Univariate*		Multivariate*,[†]	
	OR/HR[‡] (95% CI)	P Value	OR/HR[‡] (95% CI)	P Value
ACTS burden score				
TTR ≥75%[§]	1.02 (1.00–1.04)	0.018	1.01 (0.99–1.03)	0.153
TTR ≥60%[§]	1.02 (1.00–1.03)	0.017	1.01 (0.99–1.03)	0.208
Warfarin discontinuation	0.98 (0.96–1.00)	0.017	0.99 (0.97–1.01)	0.157
Overall mortality	0.99 (0.97–1.02)	0.557	0.99 (0.96–1.02)	0.515
Cardioembolic event[‖]	1.04 (0.98–1.11)	0.206	1.05 (0.99–1.10)	0.081
Major bleed	0.99 (0.96–1.01)	0.349	0.99 (0.96–1.02)	0.486
All-cause hospitalization	0.99 (0.98–1.00)	0.032	0.99 (0.98–1.00)	0.141
ACTS benefit score				
TTR ≥75%[§]	1.03 (0.99–1.07)	0.189	1.01 (0.98–1.05)	0.446
TTR ≥60%[§]	1.02 (0.99–1.06)	0.160	1.01 (0.98–1.05)	0.432
Warfarin discontinuation	1.01 (0.98–1.05)	0.440	1.00 (0.96–1.05)	0.839
Overall mortality	0.97 (0.93–1.02)	0.244	0.99 (0.95–1.03)	0.682
Cardioembolic event[‖]	1.01 (0.93–1.09)	0.897	1.04 (0.95–1.13)	0.427
Major bleed	0.96 (0.91–1.01)	0.146	0.98 (0.92–1.04)	0.435
All-cause hospitalization	0.98 (0.96–1.01)	0.163	1.00 (0.98–1.02)	0.830

*Logistic regression: time in therapeutic range (TTR); Cox proportional hazard regression: warfarin discontinuation, overall mortality, cardioembolic event, major bleed, all-cause hospitalization.
[†]Covariates: patient demographics, medical history, atrial fibrillation (AF) history, medications, functional status, care model, and region (see Table S2 for full covariate list).
[‡]Odds ratio (OR)/hazard ratio (HR) per 1-point increase in Anti-Clot Treatment Scale (ACTS) scores.
[§]Over 1 year.
[‖]Stroke/transient ischemic attack or systemic embolism.

gains by increasing the chance that therapies are selected that reduce patient burden while improving outcomes. Whether patients at high risk for dissatisfaction with warfarin therapy, identified in our cohort, would be more satisfied with non–vitamin K antagonist OACs or left atrial appendage exclusion is currently unknown. However, higher ACTS scores for patients taking non–vitamin K antagonist OACs, as compared with warfarin, have been previously reported in various cohorts.[19–21]

TTR, a quality metric for warfarin therapy[3] and determinant of outcomes,[4,5] is highly variable at the patient and site level,[14] even within integrated healthcare systems.[22] Low TTR has been associated with patient comorbidities and care pathways,[14] with little investigation into the relationship between patient-reported satisfaction with warfarin and TTR, which may be mediated through adherence. In ORBIT-AF, patient quartiles reporting less burden from warfarin therapy had higher TTR. However, after multivariate adjustment, the association was not significant. Although one interpretation of these findings is that the ACTS score has limited utility to predict TTR over the subsequent year, clinicians cannot perform in-office multivariate adjustment and the ACTS score may be a more realistic and convenient method to predict high TTR over the subsequent year. Patients predicted to have low TTR could receive more intensive INR monitoring or be considered for alternate strategies to reduce stroke risk. However, it is important to acknowledge that low TTR, caused by factors other than patient dissatisfaction, may be driving patient dissatisfaction.

ACTS scores were not associated with warfarin discontinuation, suggesting that factors other than patient satisfaction with warfarin therapy drive changes in OAC strategy. Potentially, provider preference may be the primary determinant of changes in OAC strategy, which is influenced by bleeding risk and events, frequent falls and frailty, and adherence and monitoring issues.[23] Without mediation through higher TTR and less warfarin discontinuation, patient satisfaction with warfarin therapy was not associated with clinical outcomes. Importantly, higher unadjusted risk of stroke in quartiles reporting less burden is likely attributable to the older age of patients in these quartiles, with no association between ACTS burden score and stroke in the multivariate analysis.

Study Limitations

There are several important limitations to this study. The ACTS questionnaire is not designed to provide information on individual domains of patient satisfaction and we could not assess for associations between patient acceptance (of disease or therapy), self-efficacy, or awareness and outcomes. Residual measured and unmeasured confounding could have influenced some of these findings, eg, duration of warfarin

therapy before ACTS questionnaire administration. Importantly, patients' perceived benefit and burden of OAC could have changed during follow-up, which was not accounted for by our analytic methods. Finally, the ORBIT-AF patient-reported outcomes subcohort, despite baseline characteristics suggesting similarity with all patients treated with warfarin in the ORBIT-AF cohort, may not be reflective of patients with AF at large.

Conclusions

In ORBIT AF, patient satisfaction was not associated with measurable differences in traditional metrics of anticoagulation care quality or clinical outcomes. Although patient satisfaction with warfarin does not appear to be a marker or target for improvements in TTR or warfarin discontinuation, determining patient satisfaction (or lack thereof) with OAC strategies is necessary to select therapies that minimize patient burden while improving clinical outcomes. Patients identified to be at high risk for dissatisfaction with warfarin therapy were younger and more likely to be women, have paroxysmal AF, and to be treated with antiarrhythmic drugs.

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Disclosures

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References

1. Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academic Press; 2001.

2. Rathert C, Wyrwich MD, Boren SA. Patient-centered care and outcomes: a systematic review of the literature. *Med Care Res Rev*. 2013;70:351–379.

3. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). *Circ Cardiovasc Qual Outcomes*. 2011;4:22–29.

4. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029–2037.

5. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, Albers GW. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. *Arch Intern Med*. 2007;167:239–245.

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

7. Cullen MW, Kim S, Piccini JP Sr, Ansell JE, Fonarow GC, Hylek EM, Singer DE, Mahaffey KW, Kowey PR, Thomas L, Go AS, Lopes RD, Chang P, Peterson ED, Gersh BJ; ORBIT-AF Investigators. Risks and benefits of anticoagulation in atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Circ Cardiovasc Qual Outcomes*. 2013;6:461–469.

8. Steinberg BA, Kim S, Piccini JP, Fonarow GC, Lopes RD, Thomas L, Ezekowitz MD, Ansell J, Kowey P, Singer DE, Gersh B, Mahaffey KW, Hylek E, Go AS, Chang P, Peterson ED; ORBIT-AF Investigators and Patients. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. *Circulation*. 2013;128:721–728.

9. Cano SJ, Lamping DL, Bamber L, Smith S. The Anti-Clot Treatment Scale (ACTS) in clinical trials: cross-cultural validation in venous thromboembolism patients. *Health Qual Life Outcomes*. 2012;10:120.

10. Bamber L, Wang MY, Prins MH, Ciniglio C, Bauersachs R, Lensing AW, Cano SJ. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. *Thromb Haemost*. 2013;110:732–741.

11. Prins MH, Bamber L, Cano SJ, Wang MY, Erkens P, Bauersachs R, Lensing AW. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of pulmonary embolism; results from the EINSTEIN PE trial. *Thromb Res*. 2015;135:281–288.

12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.

13. Wieloch M, Sjalander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. *Eur Heart J*. 2011;32:2282–2289.

14. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW, Hylek EM, Go AS, Piccini JP, Peterson ED; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation Investigators. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J*. 2015;170:141–148, 148.e1.

15. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.

16. Wilke T, Bauer S, Mueller S, Kohlmann T, Bauersachs R. Patient preferences for oral anticoagulation therapy in atrial fibrillation: a systematic literature review. *Patient*. 2017;10:17–37.

17. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*. 1996;156:1829–1836.

18. Wyld ML, Clayton PA, Morton RL, Chadban SJ. Anti-coagulation, anti-platelets or no therapy in haemodialysis patients with atrial fibrillation: a decision analysis. *Nephrology*. 2013;18:783–789.

19. Coleman CI, Haas S, Turpie AG, Kuhls S, Hess S, Evers T, Amarenco P, Kirchhof P, Camm AJ; XANTUS Investigators. Impact of switching from a vitamin K antagonist to rivaroxaban on satisfaction with anticoagulation therapy: the XANTUS-ACTS substudy. *Clin Cardiol*. 2016;39:565–569.

20. Hanon O, Chaussade E, Gueranger P, Gruson E, Bonan S, Gay A. Patient-reported treatment satisfaction with rivaroxaban for stroke prevention in atrial fibrillation. A French observational study, the SAFARI Study. *PLoS One*. 2016;11:e0166218.

21. Contreras Muruaga MD, Vivancos J, Reig G, Gonzalez A, Cardona P, Ramirez-Moreno JM, Marti J, Fernandez CS; ALADIN Study Investigators. Satisfaction, quality of life and perception of patients regarding burdens and benefits of vitamin K antagonists compared with direct oral anticoagulants in patients with nonvalvular atrial fibrillation. *J Comp Eff Res*. 2017;6:303–312.

22. Razouki Z, Ozonoff A, Zhao S, Jasuja GK, Rose AJ. Improving quality measurement for anticoagulation: adding international normalized ratio variability to percent time in therapeutic range. *Circ Cardiovasc Qual Outcomes*. 2014;7:664–669.

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

Table S1. Anti-Clot Treatment Scale Questionnaire
During the past 4 weeks...

1. How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in vigorous physical activities? (e.g. exercise, sports, dancing, etc.)

2. How much does the possibility of bleeding as a result of anti-clot treatment limit you from taking part in your usual activities? (e.g. work, shopping, housework etc.)

3. How bothered are you by the possibility of bruising as a result of anti-clot treatment?

4. How bothered are you by having to avoid other medicines (e.g. aspirin) as a result of anti-clot treatment?

5. How much does anti-clot treatment limit your diet? (e.g. food or drink, including alcohol)

6. How much of a hassle (inconvenience) are the daily aspects of anti-clot treatment? (e.g. remembering to take your medicine at a certain time, taking the correct dose of your medicine, following a diet, limiting alcohol, etc.)

7. How much of a hassle (inconvenience) are the occasional aspects of anti-clot treatment? (e.g. the need for blood tests, going to or contacting the clinic/doctor, making arrangements for treatment while travelling etc.)

Now I want to ask you about daily and occasional aspects of your ACT during the past 4 weeks!.

8. How difficult is it to follow your anti-clot treatment?

9. How time-consuming is your anti-clot treatment?

10. How much do you worry about your anti-clot treatment?

11. How frustrating is your anti-clot treatment?

12. How much of a burden is your anti-clot treatment?

13. Overall, how much of a negative impact has your anti-clot treatment had on your life?

14. How confident are you that your anti-clot treatment will protect your health? (e.g. prevent blood clots, stroke, heart attack, DVT, embolism)

15. How reassured do you feel because of your anti-clot treatment?

16. How satisfied are you with your anti-clot treatment?

17. <u>Overall, how much of a positive impact has your anti-clot treatment had on your life?</u>

ACTS Burdens scale: questions 1-12
ACTS benefits scale: questions 14-16
Questions 13 and 17 are global response question
Patients respond on a 1-5 Likert scale (higher score corresponds to higher satisfaction)

Table S2. Multivariate Model Covariates

1) Demographics
    a. Age: years
    b. Gender: male/female
    c. Level of education: some school/high school graduate/college graduate/post graduate
    d. Payor/Insurance: Medicare or Medicaid/private/other

2) Medical History
    a. Smoking: current/recent or former/non-smoker
    b. Cancer: yes/no
    c. Hypertension: yes/no
    d. Diabetes: yes/no
    e. GI bleed: yes/no
    f. Obstructive sleep apnea: yes/no
    g. Dialysis: yes/no
    h. Hyperlipidemia: yes/no
    i. Anemia: yes/no
    j. Cognitive impairment/dementia: yes/no
    k. Frailty: yes/no
    l. COPD: yes/no

3) Atrial Fibrillation (AF) History
    a. Type of AF: first detected or new onset/paroxysmal/persistent/permanent
    b. AF duration

4) Coronary Artery Disease (CAD) History
    a. History of coronary artery disease: yes/no
    b. Prior MI: yes/no
    c. Prior PCI: yes/no

5) Cardiovascular History (non-AF/CAD)
    a. Peripheral vascular disease: yes/no
    b. Stroke or TIA: yes/no
    c. Congestive heart failure (CHF): no CHF/NYHA class I/NYHA class II/ NYHA class III&IV
    d. Significant valvular disease: yes/no
    e. Prior valve replacement/repair: yes/no

6) Echocardiographic Assessment (TTE or TEE)
    a. LVEF: normal (≥50%)/mild dysfunction (>40%, <50%)/moderate dysfunction (≥30%, ≤40%)/severe dysfunction (<30%)
    b. LAD type: normal/mild enlargement/moderate enlargement/severe enlargement

7) Pharmacotherapy
    a. Current aspirin use: yes/no
    b. Current clopidogrel use: yes/no
    c. Prior antiarrhythmic drug use: yes/no

8) Vital Signs
    a. Height, cm
    b. Diastolic blood pressure, mmHg
    c. Systolic blood pressure, mmHg
    d. Body mass index, kg/m²

9) Laboratory Data
    a. eGFR, mg/dL (MDRD)
    b. Hematocrit, %

10) Functional Status
    a. Functional status: living independently/living with assistance, resides in assisted living facility or in skilled nursing home, or bedbound

11) Provider or Site
    a. PI/site specialty: cardiology/electrophysiology/family practice or internal medicine
    b. Region: northeast/east/midwest/west

Table S3. Baseline Characteristics of ORBIT-AF Patients on Warfarin By Study Inclusion Status*

Demographics	Total (N=7,215)	Excluded (N=5,701)	Included (N=1,514)	P value[†]
Age (mean±SD)	74.2±10.2	74.1±10.3	74.5±9.8	0.252
Female (%)	3057 (42.4)	2416 (42.4)	641 (42.3)	0.798
Race				
White (%)	6443 (89.3)	5065 (88.8)	1378 (91.0)	<0.001
$CHADS_2$ Score Group (%)				0.003
0-1	1700 (23.6)	1299 (22.8)	401 (26.5)	
≥2	5515 (76.4)	4402 (77.2)	1113 (73.5)	
$CHADS_2$ Score (mean±SD)	2.4±1.3	2.4±1.3	2.3±1.3	<0.001
CHA_2DS_2-VASc Score (mean±SD)	4.1±1.7	4.1±1.7	3.9±1.7	<0.001
Non-Paroxysmal AF (%)	3665 (50.8)	2931 (51.4)	734 (48.5)	<0.001

*Inclusion required ACTS questionnaire completion and follow-up available, †Differences between excluded and included patients assessed using the chi-squared test and Wilcoxon rank-sum test for categorical and continuous variables, respectively
ACTS: anti-clot treatment scale, AF: atrial fibrillation

Table S4. Baseline Characteristics by ACTS Benefit Score Quartile

	ACTS Benefit Score (N=1,513)					
	Total (N=1,513)	Quartile 1 (N=310)	Quartile 2 (N=379)	Quartile 3 (N=492)	Quartile 4* (N=332)	P value†
ACTS Score (mean±SD)	10.7±3.4	5.2±1.9	9.8±0.8	12.2±0.4	14.8±0.4	<0.001
Demographics						
Age (mean±SD)	74.5±9.8	74.5±9.6	73.0±10.3	75.3±9.7	75.2±9.3	0.004
Female (%)	641 (42.4)	132 (42.6)	169 (44.6)	214 (43.5)	126 (38.0)	0.298
Race						0.306
White (%)	1377 (91.0)	282 (91.6)	346 (91.3)	438 (89.0)	311 (93.7)	
CHADS$_2$ Score Group (%)						0.437
0-1	401 (26.5)	81 (26.1)	104 (27.4)	120 (24.4)	96 (28.9)	
≥2	1112 (73.5)	229 (73.9)	275 (72.6)	372 (75.6)	236 (71.1)	
CHADS$_2$ Score (mean±SD)	2.3±1.3	2.3±1.2	2.3±1.3	2.3±1.3	2.2±1.2	0.764
CHA$_2$DS$_2$-VASc Score (mean±SD)	3.9±1.7	4.0± 1.6	4.0± 1.8	4.0± 1.7	3.8±1.6	0.612
Non-Paroxysmal AF (%)	734 (48.5)	146 (47.1)	184 (48.6)	238 (48.4)	166 (50.0)	0.580
Heart Failure (%)	427 (28.2)	87 (28.1)	116 (30.6)	133 (27.0)	91 (27.4)	0.678
CKD (%)	525 (34.7)	105 (37.2)	130 (36.6)	171 (38.7)	119 (39.3)	0.884
Coronary Artery Disease (%)	478 (31.6)	109 (35.2)	113 (29.8)	162 (32.9)	94 (28.3)	0.218
Myocardial Infarction (%)	212 (14.0)	48 (15.5)	51 (13.5)	63 (12.8)	50 (15.1)	0.670
Stroke/TIA (%)	254 (16.8)	43 (13.9)	74 (19.5)	87 (17.7)	50 (15.1)	0.178
Peripheral Artery Disease (%)	186 (12.3)	36 (11.6)	44 (11.6)	69 (14.0)	37 (11.1)	0.558
Diabetes (%)	416 (27.5)	100 (32.3)	108 (28.5)	129 (26.2)	79 (23.8)	0.094
Hypertension (%)	1268 (83.8)	264 (85.2)	324 (85.5)	411 (83.5)	269 (81.0)	0.372
Anemia (%)	225 (14.9)	48 (15.5)	52 (13.7)	75 (15.2)	50 (15.1)	0.907
GI Bleed (%)	100 (6.6)	25 (8.1)	22 (5.8)	27 (5.5)	26 (7.8)	0.352
Care Model						
Payor/Insurance (%)						0.075
Medicaid/Medicare	1116 (73.8)	236 (76.1)	265 (69.9)	369 (75.0)	246 (74.1)	
Private	319 (21.1)	61 (19.7)	96 (25.3)	89 (18.1)	73 (22.0)	
Other	78 (5.2)	13 (4.2)	18 (4.8)	34 (6.9)	13 (3.9)	
OAC Management (%)						
Home INR Monitoring	46 (3.0)	6 (1.9)	15 (4.0)	12 (2.4)	13 (3.9)	0.280
Anticoagulation Clinic	601 (39.7)	140 (45.2)	142 (37.5)	198 (40.2)	121 (36.5)	0.103
Cardiology Care (%)	1265 (83.6)	254 (81.9)	322 (85.0)	419 (85.2)	270 (81.3)	0.352
Medication Use						
Prior Warfarin Use‡ (%)	1397 (92.3)	288 (92.9)	341 (90.0)	458 (93.1)	310 (93.4)	0.258
Beta Blockers (%)	1015 (67.1)	195 (62.9)	252 (66.5)	336 (68.3)	232 (69.9)	0.287
Calcium Channel Blockers§ (%)	250 (16.5)	62 (20.0)	71 (18.7)	65 (13.2)	52 (15.7)	0.041
Digoxin (%)	387 (25.6)	89 (28.7)	95 (25.1)	133 (27.0)	70 (21.1)	0.121
Amiodarone (%)	125 (8.3)	28 (9.0)	22 (5.8)	47 (9.6)	28 (8.4)	0.225
Rhythm Control Agents (%)	384 (25.4)	78 (25.2)	89 (23.5)	130 (26.4)	87 (26.2)	0.770
Anti-Platelet Agents (%)	558 (36.9)	111 (35.8)	139 (36.7)	189 (38.4)	119 (35.8)	0.847
Statins (%)	789 (52.2)	171 (55.2)	184 (48.6)	269 (54.7)	165 (49.7)	0.152

*ACTS score quartile with greatest benefit, †Differences between quartiles assessed using the chi-squared test and Kruskal-Wallis test for categorical and continuous variables, respectively, ‡Prior to enrollment in ORBIT-AF, §Non-dihydropyridine calcium channel blockers

ACTS: anti-clot treatment scale, AF: atrial fibrillation, INR: international normalized ratio, CKD: chronic kidney disease, TIA: transient ischemic attack

Table S5. Association of ACTS Scores with Warfarin and AF Outcomes in Patients with CHA$_2$DS$_2$-VASc ≥ 4

ACTS Burden Score

	Univariate*		Multivariate*,†	
	OR/HR‡ (95% CI)	P Value	OR/HR‡ (95% CI)	P Value
TTR ≥ 75%§	1.03 (1.00 - 1.05)	0.022	1.02 (1.00 - 1.05)	0.072
TTR ≥ 60%§	1.02 (1.00 - 1.03)	0.064	1.01 (0.98 - 1.03)	0.586
Warfarin Discontinuation	0.98 (0.95 - 1.00)	0.044	0.98 (0.95 - 1.01)	0.177
Overall Mortality	0.99 (0.96 - 1.01)	0.382	0.99 (0.96 - 1.02)	0.494
Cardioembolic Event‖	1.04 (0.97 - 1.12)	0.261	1.03 (0.96 - 1.11)	0.399
Major Bleed	1.00 (0.96 - 1.04)	0.943	0.99 (0.94 - 1.04)	0.299
All-Cause Hospitalization	0.99 (0.98 - 1.00)	0.192	0.99 (0.98 - 1.00)	0.114

ACTS Benefit Score

	Univariate*		Multivariate*,†	
	OR/HR‡ (95% CI)	P Value	OR/HR‡ (95% CI)	P Value
TTR ≥ 75%§	1.02 (0.97 - 1.07)	0.499	1.00 (0.94 - 1.07)	0.930
TTR ≥ 60%§	1.01 (0.96 - 1.07)	0.661	1.01 (0.95 - 1.08)	0.743
Warfarin Discontinuation	1.03 (0.96 - 1.10)	0.408	1.03 (0.94 - 1.12)	0.530
Overall Mortality	0.98 (0.93 - 1.03)	0.397	0.95 (0.91 - 1.00)	0.047
Cardioembolic Event‖	1.09 (0.96 - 1.24)	0.179	1.15 (0.98 - 1.35)	0.082
Major Bleed	0.98 (0.90 - 1.07)	0.648	1.01 (0.92 - 1.11)	0.865
All-Cause Hospitalization	0.99 (0.96 - 1.01)	0.353	0.99 (0.96 - 1.02)	0.612

*Logistic regression: TTR; Cox proportional hazard regression: Warfarin discontinuation, Overall mortality, Cardioembolic event, Major bleed, All-cause hospitalization, †Covariates: patient demographics, medical history, AF history, medications, functional status, care model, and region (see Supplemental Table 2 for full covariate list), ‡OR/HR per 1-point increase in ACTS scores; §Over 1 year, ‖Stroke/transient ischemic attack or systemic embolism

ACTS: anti-clot treatment scale, AF: atrial fibrillation, OAC: oral anticoagulation, TTR: time in therapeutic range

Table S6. Association of ACTS Scores with Warfarin and AF Outcomes in Patients with CHA$_2$DS$_2$-VASc < 4

ACTS Burden Score

	Univariate*		Multivariate*,†	
	OR/HR‡ (95% CI)	P Value	OR/HR‡ (95% CI)	P Value
TTR ≥ 75%§	1.01 (0.98 - 1.04)	0.686	1.00 (0.97 - 1.03)	0.878
TTR ≥ 60%§	1.01 (0.99 - 1.04)	0.312	1.00 (0.97 - 1.04)	0.814
Warfarin Discontinuation	0.98 (0.96 - 1.00)	0.092	1.00 (0.97 - 1.03)	0.999
Overall Mortality	1.03 (0.94 - 1.12)	0.575	1.08 (0.94 - 1.25)	0.290
Cardioembolic Event‖	1.03 (0.94 - 1.14)	0.509	-	-
Major Bleed	0.97 (0.93 - 1.01)	0.123	0.95 (0.88 - 1.02)	0.164
All-Cause Hospitalization	0.99 (0.97 - 1.00)	0.057	0.99 (0.98 - 1.01)	0.589

ACTS Benefit Score

	Univariate*		Multivariate*,†	
	OR/HR‡ (95% CI)	P Value	OR/HR‡ (95% CI)	P Value
TTR ≥ 75%§	1.03 (0.97 - 1.09)	0.310	1.03 (0.97 - 1.10)	0.347
TTR ≥ 60%§	1.04 (0.98 - 1.09)	0.167	1.04 (0.97 - 1.11)	0.266
Warfarin Discontinuation	0.99 (0.94 - 1.05)	0.745	0.99 (0.92 - 1.06)	0.695
Overall Mortality	1.06 (0.94 - 1.20)	0.351	1.14 (0.84 - 1.54)	0.406
Cardioembolic Event‖	0.94 (0.82 - 1.09)	0.441	-	-
Major Bleed	0.91 (0.83 - 1.00)	0.042	0.89 (0.79 - 1.01)	0.071
All-Cause Hospitalization	0.99 (.095 - 1.02)	0.494	1.00 (0.97 - 1.04)	0.969

*Logistic regression: TTR; Cox proportional hazard regression: Warfarin discontinuation, Overall mortality, Cardioembolic event, Major bleed, All-cause hospitalization, †Covariates: patient demographics, medical history, AF history, medications, functional status, care model, and region (see Supplemental Table 2 for full covariate list), ‡OR/HR per 1-point increase in ACTS scores; §Over 1 year, ‖Stroke/transient ischemic attack or systemic embolism

ACTS: anti-clot treatment scale, AF: atrial fibrillation, OAC: oral anticoagulation, TTR: time in therapeutic range