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Incremental prognostic value of renal function for stroke prediction in atrial fibrillation☆

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ABSTRACT

Background: Renal function has been associated with an increased stroke risk in patients with atrial fibrillation (AF). However, whether renal function incrementally adds to risk prediction in both anticoagulated and non-anticoagulated patients with AF is unclear.

Methods: We used data from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF)—a national, prospective, outpatient AF registry in patients aged >18 years (2010—2011). The association between baseline renal function and risk of stroke/systemic embolism (SSE) was evaluated in proportional hazards models adjusting for stroke risk score components. We compared discrimination of 2-year outcomes using C-indices and evaluated calibration by comparing event rates in ORBIT-AF to published rates from an external clinical trial population (ROCKET AF) and an observational cohort (ATRIA).

Results: Among 9743 patients included in the analysis, the median age was 75 years (interquartile range [IQR] 67–82), 89.5% were white, 43% were female, and 76% were taking oral anticoagulation (OAC). Over a median follow-up of 2.3 years, 214 SSE events occurred (1.00 per 100 patient-years). Continuous creatinine clearance (CrCl) was not associated with SSE risk after adjusting for other clinical factors (components of $CHADS_2$ or CHA_2DS_2-VASc). Discrimination for predicting stroke (C-index; 95% CI) was similar for R_2CHADS_2 (0.65; 0.61–0.69), $CHADS_2$ (0.65; 0.61–0.69), and CHA_2DS_2-VASc (0.66; 0.62–0.70).

Conclusions and relevance: In a community patient population with AF, renal dysfunction was not independently associated with embolic risk beyond other established risk factors in either OAC-treated or untreated patients. Additional study is needed to identify clinical factors that incrementally add to stroke risk prediction.

1. Introduction

Optimal management of stroke risk in atrial fibrillation (AF) depends upon accurate stroke risk assessment. The R_2CHADS_2 score was developed in the Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial population[1] to improve risk stratification by accounting for impaired renal function, a known risk factor for ischemic stroke in AF [2, 3]. In anticoagulated ROCKET AF patients, renal function as a continuous variable was highly associated with the occurrence of stroke/systemic embolism (SSE) after adjustment for known predictors of stroke [4]. While additional validation results have been mixed [5–9], results from a recent meta-analysis suggest that renal impairment is significantly associated with increased stroke risk, independent of other $CHADS_2$ risk factors [10]. More data are needed on the incremental predictive value of continuous and categorical renal function relative to existing stroke risk scores, in addition to how score performance varies by anticoagulation status in contemporary populations. We evaluated the association of continuous renal function with SSE in a large, contemporary, nationwide AF registry

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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among oral anticoagulation (OAC)-treated and untreated patients. Additionally, we compared predictive performance of R_2CHADS_2, $CHADS_2$, and CHA_2DS_2-VASc scores overall and by anticoagulation status.

2. Methods

2.1. Study population

We used data from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) study. Details of the ORBIT-AF study design have been described [11]. Briefly, ORBIT-AF was a national, prospective, outpatient registry of incident and prevalent AF. Patients aged 18 years or older with electrocardiographically confirmed AF provided informed consent and were enrolled at 176 sites in the United States. Clinical sites were recruited to represent a variety of practice specialties, including cardiology, electrophysiology, and primary care, and to represent diverse geographical regions. ORBIT-AF sites abstracted demographic and clinical data, including disease history, comorbidities, current therapeutic strategies, and practice characteristics, and entered data into an interactive, web-based form. At approximately 6-month intervals, sites collected and entered information on patient vital status, hospitalizations, stroke and bleeding events, medical therapies, procedures, disease progression, and quality of life. Patients were followed-up for 24 to 36 months. Because stroke risk scores may be useful for both evaluation of stroke risk before initiating treatment and identifying residual risk among patients on OAC [4,6,12,13], we evaluated associations of continuous renal function and SSE as well as score performance overall and separately among patients who were OAC-treated and those who were not. All stroke events occurring in the ORBIT-AF study were verified by single-source document submission (e.g., hospital discharge report) and centralized physician review at the Duke Clinical Research Institute, which served as the data coordinating center [11]. Study oversight and management was provided by the Duke Clinical Research Institute.

2.2. Risk score calculation

Stroke risk scores were calculated using data from the baseline visit. The $CHADS_2$ score was calculated as follows: 2 points for a history of prior stroke or transient ischemic attack (TIA) and 1 point each for heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years, and diabetes (range: 0–6). The CHA_2DS_2-VASc score was calculated by assigning 2 points each for age ≥ 75 years and history of stroke/TIA, and 1 point each for heart failure/left ventricular dysfunction, hypertension, diabetes, 65 ≤ age ≤ 74 years, female sex, and vascular disease (range: 0–9) [14]. R_2CHADS_2 was calculated similarly to the $CHADS_2$ score, with the addition of 2 points for impaired renal function (creatinine clearance [CrCl] < 60 mL/min) [4].

2.3. Outcome definition

The primary outcome used in regression models was SSE [11]. This endpoint was used to stay consistent with the endpoint used in development of the R_2CHADS_2 score. Because of potential heterogeneity in etiology of the SSE endpoint, we examined the association between impaired renal function and ischemic stroke only in a sensitivity analysis.

2.4. Statistical analysis

We compared baseline characteristics at study enrollment by occurrence of SSE over all available follow-up. Categorical variables are presented as frequencies (percentages), and differences between groups were assessed by the chi-square test. Continuous variables are presented as medians (interquartile ranges [IQRs]), and differences between groups were assessed using the Wilcoxon rank-sum test.

Given variation in CrCl cutpoints used for classifying impaired renal function in previous work, in addition to the potential for heterogeneity within broadly defined renal function categories, we first evaluated the association between continuous CrCl allowing for non-linearity and SSE prior to dichotomizing. We then examined the association between impaired renal function and risk of SSE using the CrCl cutpoints as defined in the original R_2CHADS_2 score development analysis (CrCl < 60 mL/min; estimated from the Cockcroft-Gault formula). We used the Cockcroft-Gault estimation, since it is the method used to determine anticoagulant dosing in pivotal clinical trials and is recommended by the U.S. Food and Drug Administration. For adjusted models, we included components of the $CHADS_2$ and CHA_2DS_2-VASc scores. Cox proportional hazards models with robust standard errors to account for within-site clustering were used for all regression analyses. Missing data were handled with single imputation, and imputed values were obtained by Markov Chain Monte Carlo (MCMC) or regression methods.

We compared the performance of the R_2CHADS_2 score to that of the 2 existing stroke risk scores with regard to discrimination and calibration of events over a 2-year follow-up period to promote consistency with the R_2CHADS_2 development analysis. To estimate discrimination, we calculated C-statistics and 95% confidence intervals (CIs), accounting for censoring [15]. We then constructed a calibration plot displaying the 2-year event rates and 95% CIs observed in the ORBIT-AF cohort and those previously published from the original derivation cohorts for each point value. Good calibration exists when the event rates in the validation cohort correspond closely to the published event rates in the derivation cohort.

As an additional summary of incremental value, we aimed to evaluate R_2CHADS_2 via the net reclassification index (NRI). This method has been used to evaluate R_2CHADS_2 and many other risk scores in cardiology [4,8,16–18]. The result was inconsistent with other metrics of added value (leading to opposite conclusions); therefore, we engaged methodological experts, including the original author of the NRI, to understand this phenomenon. Numerous pitfalls were identified, including that the NRI can favor a poorly calibrated model (or risk score) and is sensitive to decisions about risk thresholds. Here, we illustrate these phenomena using a clinical example comparing performance of R_2CHADS_2, $CHADS_2$, and CHA_2DS_2-VASc. First, we categorized risk scores into low, medium, and high using point thresholds from prior publications:

1. *Prior guidelines and/or original derivation* ($CHADS_2$: low = 0, medium = 1, high = 2+; CHA_2DS_2-VASc: low = 0, medium = 1, high = 2+; R_2CHADS_2 (low = 0–3, medium = 4–5, high = 6+); denoted NRI (prior).
2. *Derivation of R_2CHADS_2 in ROCKET AF* ($CHADS_2$: low = 0–3, medium = 4–5, high = 6+; CHA_2DS_2-VASc: low = 0–4, medium = 5–6, high = 7+; R_2CHADS_2 (low = 0–3, medium = 4–5, high = 6+), denoted NRI (ROCKET AF).

Second, we defined categories based on well-calibrated, common risk thresholds applied to ORBIT-AF:

1. *Three categories* (low ≤2%, medium = 2–4%, high = 4%+, 2-year event rate), denoted NRI (2%, 4%).
2. *Two categories above and below the ORBIT-AF 2-year event rate* (2%), denoted NRI (2%).

All p-values presented are 2-sided; $p < 0.05$ was considered to be statistically significant for all analyses. All statistical analyses were performed using SAS software (version 9.3, Cary, NC). All ORBIT-AF study participants gave written informed consent prior to enrollment. The ORBIT-AF registry was approved by the Duke Institutional Review Board (IRB), and all participating clinical sites obtained approval from local IRBs prior to entering patient data.

Table 1
Baseline characteristics of the ORBIT-AF population by stroke occurrence in full follow-up.

Variable	No stroke ($N = 9529$)	Stroke (N = 214)	P-Value*
Age, yrs., median (IQR)	75.0 (67.0–82.0)	80.0 (73.0–84.0)	<0.0001
White race	89.5	86.5	0.08
Female sex	42.3	55.1	0.0002
Medical history			
Cancer	23.7	28.5	0.1008
Anemia	18.3	28.5	0.0001
Frailty	5.8	10.3	0.006
COPD	16.4	20.6	0.10
Hypertension	82.9	93.9	<0.0001
Diabetes	29.5	31.3	0.55
CKD	34.3	42.1	0.11
Smoking	48.3	50.5	0.54
Prior stroke	8.6	23.8	<0.0001
CHF	32.7	40.2	0.02
Prior MI	16.0	19.2	0.21
CrCl, median, mL/min, median (IQR)	69.7 (50.4–97.0)	61.2 (41.9–77.5)	<0.0001
CrCl < 60 mL/min	35.1	47.7	0.002
OAC use	76.4	75.7	0.81
$CHADS_2$			
0	6.4	1.9	<0.0001
1	21.8	9.4	
2	33.0	28.5	
3	22.9	22.9	
4	10.1	21.0	
5	4.5	13.1	
6	1.3	3.3	
CHA_2DS_2-VASc			<0.0001
0	2.2	0.0	
1	6.8	3.3	
2	12.3	3.3	
3	18.7	12.6	
4	23.6	21.0	
5	18.6	22.0	
6	10.6	16.4	
7	5.0	13.6	
8	1.9	6.1	
9	0.4	1.9	
ATRIA bleeding score, median (IQR)	3.0 (1.0–4.0)	3.0 (3.0–6.0)	<0.0001

Abbreviations: ATRIA, Anticoagulation and Risk Factors in Atrial Fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; OAC, oral anticoagulation.

* P-values from chi-squared tests for categorical variables and Wilcoxon-rank sum tests for continuous variables.

3. Results

From 2010 to 2011, 10,135 patients were enrolled at 176 ORBIT-AF sites. After excluding patients without follow-up data ($N = 392$), our final analytic population was 9743 patients. Over a median follow-up of 2.3 years (IQR 1.8–2.9), $N = 214$ SSE events occurred (event rate 1.0 [95% CI 0.88–1.15] events per 100 patient-years); 76.4% percent of the population was treated with an OAC at baseline. In the ORBIT-AF study population, CrCl was <15 mL/min in 0.5% of patients, 15–29 mL/min in 4.6%, 30–45 mL/min in 12.6%, 45–60 mL/min in 17.7%, and ≥ 60 mL/min in 57.1% of patients (7.6% of patients had a missing value for CrCl).

The distributions of baseline characteristics by occurrence of SSE over follow-up are shown in Table 1. Of 214 SSE events, 177 were ischemic strokes and 37 were hemorrhagic strokes. Patients who experienced SSE were older and more likely to be female compared with those who did not. Medical comorbidities, including prior stroke, anemia, frailty, hypertension, and heart failure, were more common among patients who experienced a stroke compared with those who did not. Relative to those who did not experience SSE, patients experiencing SSE had diminished renal function with a lower median CrCl (61.2 vs. 69.7 mL/min; $p < 0.0001$) and were more likely to have CrCl < 60 mL/min (47.7% vs. 35.1%; $p = 0.002$).

Results from multivariable modeling are displayed in Table 2. In multivariable models with a term for continuous CrCl allowing for non-linearity, there was no significant association (HR; 95% CI) of renal function with SSE in models with components of $CHADS_2$ (per 5 mL/min increase = 0.98; 0.95–1.00) or CHA_2DS_2-VASc (per 5 mL/min increase = 0.98; 0.96–1.01). Following dichotomization of CrCl, impaired renal function was not significantly associated with SSE in models adjusting for components of $CHADS_2$ (1.09; 0.79–1.50) or CHA_2DS_2-VASc (0.98; 0.71, 1.35); results were consistent across strata of baseline OAC use. Event rates according to $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc, by OAC status, are reported in Supplemental Table 1. Not surprisingly, event rates are lower among patients taking OAC. However, score discrimination (C-statistics and 95% CIs) was similar for $CHADS_2$, R_2CHADS_2, and CHA_2DS_2-VASc (Table 3) among both OAC-treated patients and those not receiving OAC. In a sensitivity analysis, we repeated regression models using ischemic stroke as the outcome of interest; results were similar to models with SSE as the outcome (Supplemental Table 2). Associations were similar in models of ischemic stroke and categorized renal function (CrCl < 60 mL/min) or continuous renal function, and when adjusting for components of $CHADS_2$ or CHA_2DS_2-VASc.

Table 3
C-index of stroke risk scores overall and by OAC status calculated at 2 years.

Stroke Risk Score	Overall C-index (95% CI)	OAC[a] C-index (95% CI)	No OAC C-index (95% CI)
$CHADS_2$	0.65 (0.61–0.69)	0.64 (0.59–0.69)	0.70 (0.63–0.78)
CHA_2DS_2-VASc	0.66 (0.62–0.70)	0.64 (0.59–0.69)	0.71 (0.65–0.78)
R_2CHADS_2	0.65 (0.61–0.69)	0.63 (0.58–0.68)	0.70 (0.62–0.77)

Abbreviations: CI, confidence interval; OAC, oral anticoagulation.
[a] OAC defined as warfarin or dabigatran use at baseline. Discrimination based on the ordinal points assigned by each score.

The calibration of R_2CHADS_2 is shown in Fig. 1, which displays the observed event rates by R_2CHADS_2 scores as well as published event rates from ROCKET AF and ATRIA cohorts. Increasing event rates were observed for each increase in the R_2CHADS_2 score in all cohorts. However, the SSE event rates were significantly lower in the ORBIT-AF cohort than in the ROCKET AF or ATRIA cohorts for each score value (ROCKET stroke rates 1.3–2.5 times ORBIT-AF stroke rates; ATRIA stroke rates 2.2–4.2 times ORBIT-AF stroke rates).

The results of the net reclassification analysis depended on how scores were categorized. In contrast to what was observed in models with continuous renal function, the NRI based on guideline thresholds (NRI [prior]) comparing R_2CHADS_2 to $CHADS_2$ suggests that renal function provides incremental value, with a value of 0.11 (95% CI 0.03–0.18). Similarly, the NRI (prior) for R_2CHADS_2 versus CHA_2DS_2-VASc was 0.13 (95% CI 0.05–0.19) (Table 4). Using the classifications proposed by ROCKET AF for all 3 scores, the NRI remained positive when comparing R_2CHADS_2 to $CHADS_2$ (NRI [ROCKET] = 0.15 [95% CI 0.08–0.22]), but not when comparing R_2CHADS_2 to CHA_2DS_2-VASc (NRI [ROCKET] = 0.01 [95% CI −0.09–0.11]).

Importantly, the preceding thresholds were not calibrated to the ORBIT-AF data nor consistent across scores with respect to event rates (Supplemental Table 1). Classifying scores at the observed 2-year event rate (2%), no incremental value of R_2CHADS_2 was observed when compared with $CHADS_2$ (NRI [2%] = 0.0 [95% CI −0.08–0.08]) or CHA_2DS_2-VASc (NRI [2%] = −0.02 [95% CI −0.09–0.06]). Results for the well-calibrated, 3-category NRI (2%, 4%) were similar (Table 4).

4. Discussion

We examined the incremental prognostic value of renal function in stroke prediction in a contemporary, outpatient nationwide AF population. We found that impaired renal function (defined continuously or

Table 2
Association between impaired renal function and stroke or systemic embolism in models with terms for $CHADS_2$ and CHA_2DS_2–VASc.

Adjustment strategy	Covariate	Overall		OAC-Treated		Untreated	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
$CHADS_2$ components	History of stroke/TIA	2.67 (1.97–3.61)	<0.0001	2.65 (1.89–3.72)	<0.0001	2.89 (1.49–5.58)	0.0016
	History of hypertension	2.64 (1.54–4.53)	0.0004	2.12 (1.16–3.88)	0.0140	6.01 (1.47–24.58)	0.0125
	Age ≥ 75 years	1.58 (1.07–2.33)	0.0222	1.63 (1.06–2.51)	0.0267	1.48 (0.73–3.00)	0.2731
	History of heart failure	1.19 (0.90–1.57)	0.2141	1.26 (0.91–1.76)	0.1674	1.01 (0.58–1.76)	0.9761
	History of diabetes	1.04 (0.79–1.38)	0.7556	1.09 (0.78–1.52)	0.6120	0.91 (0.54–1.53)	0.7202
	Continuous renal function (per 5 mL/min)	0.98 (0.95–1.00)	0.0723	0.98 (0.95–1.01)	0.1218	0.98 (0.92–1.03)	0.4381
CHA_2DS_2-VASc components	History of stroke/TIA	2.61 (1.92–3.53)	<0.0001	2.60 (1.85–3.65)	<0.0001	2.77 (1.43–5.39)	0.0026
	History of hypertension	2.54 (1.48–4.36)	0.0007	2.03 (1.11–3.72)	0.0210	5.79 (1.41–23.79)	0.0148
	Female (vs. male)	1.41 (1.05–1.90)	0.0206	1.50 (1.03–2.18)	0.0331	1.18 (0.68–2.07)	0.5531
	Age ≥ 75 (vs. age < 65) years	1.69 (0.96–2.98)	0.0705	1.82 (0.91–3.64)	0.0906	1.63 (0.68–3.93)	0.2725
	History of heart failure	1.19 (0.89–1.58)	0.2371	1.28 (0.91–1.80)	0.1492	0.96 (0.53–1.74)	0.9021
	History of vascular disease	1.16 (0.89–1.51)	0.2672	1.11 (0.84–1.48)	0.4615	1.27 (0.64–2.51)	0.4902
	65 ≤ age < 75 (vs. age < 65) years	1.11 (0.66–1.85)	0.6900	1.16 (0.62–2.15)	0.6483	1.19 (0.49–2.90)	0.7055
	History of diabetes	1.03 (0.78–1.37)	0.8146	1.08 (0.78–1.52)	0.6347	0.89 (0.52–1.51)	0.6604
	Continuous renal function (per 5 mL/min)	0.98 (0.96–1.01)	0.2503	0.99 (0.96–1.02)	0.3854	0.98 (0.93–1.04)	0.5742

Abbreviations: CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.

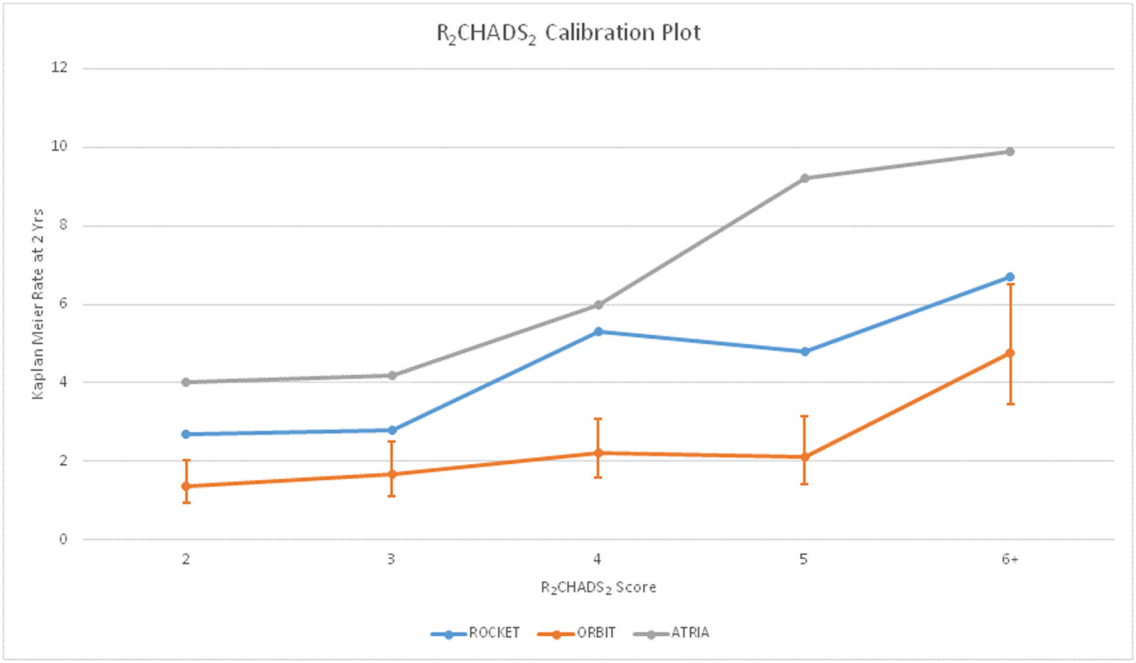

Fig. 1. Calibration of R_2CHADS_2 in ROCKET AF, ORBIT-AF, and ATRIA cohorts.

using a binary cutpoint of CrCl <60 mL/min) was not independently associated with increased risk of SSE in models adjusting for the components of $CHADS_2$ or CHA_2DS_2-VASc in the ORBIT-AF population. All 3 risk scores had similar, modest discrimination for predicting ischemic stroke at 2 years in the overall population. Discrimination for all scores was modest in both OAC-treated and untreated patients.

Since 2001, the $CHADS_2$ score has been the most widely used AF stroke risk classification scheme in clinical practice. However, because patients in low-risk strata according to $CHADS_2$ have an absolute stroke risk of 2% per year [19], in 2014 U.S. guidelines began to recommend the use of CHA_2DS_2-VASc due to the gains in discrimination for patients with $CHADS_2 = 1$ [20]. While this recommendation is supported by reports of superior discrimination among low-risk patients with CHA_2DS_2-VASc [21], neither $CHADS_2$ nor CHA_2DS_2-VASc has shown consistently high predictive performance, and guideline authors acknowledged that "evolution of AF-related thromboembolic risk evaluation is needed." [21] The R_2CHADS_2 score was developed in the ROCKET AF trial population[4] to improve risk stratification by accounting for impaired renal function, a known risk factor for ischemic stroke in AF [2, 3]. In the anticoagulated ROCKET AF population, renal function was strongly significant in a multivariable model for SSE. However, given that ROCKET AF was an international clinical trial including patients with higher baseline stroke risk who were all taking anticoagulants [1], external validations are needed to assess the generalizability of these findings to other AF populations, where undertreatment among indicated patients is common.

Prior work has indicated the potential importance of impaired renal function for the prediction of SSE in AF. In another study of 547 catheter ablation patients, Chao and colleagues found that adding a term for renal dysfunction significantly improved the predictive accuracy of CHA_2DS_2-VASc, with an increase in the C-statistic from 0.84 to 0.88 ($p = 0.043$) [5]. However, a more recent analysis from the same investigative group found the opposite result [22]. Another analysis of pooled clinical trial data demonstrated the independent predictive value of CrCl among OAC-treated patients [23]. However, these results contrast those observed in multiple other studies, each of which found little to no improvement in risk score discrimination after addition of a term for renal function to existing scores [6–9]. A recent meta-analysis of >500,000 patients in 18 studies reported that renal impairment was independently associated with significantly increased risk of thromboembolic events that persisted after adjusting for $CHADS_2$ risk factors [10]. However, this analysis did not examine the incremental predictive value of renal function to the CHA_2DS_2-VASc score, and the improvement in risk discrimination with the addition of renal impairment to $CHADS_2$ was moderate (Δ in C-index = 0.03).

Evidence from our study suggests that renal function had limited incremental predictive value beyond CHA_2DS_2 or CHA_2DS_2-VASc. The ORBIT-AF population is well-treated with respect to anticoagulant use, and SSE rates at each level of CHA_2DS_2-VASc are lower than event rates from the original development population for the score. This lack of calibration complicates the interpretation of the NRI, which can favor poorly calibrated risk functions [24,25]. The positive NRI for R_2CHADS_2, originally found in ROCKET AF and a companion validation sample [26] can be replicated in ORBIT-AF. However, this result depends on the cutpoints used for low-, medium-, and high-risk categories and conflicts with the results of multivariable modeling. The wide differences in the results of the NRI analyses depending on risk thresholds underscore the potential pitfalls of comparing categorical risk scores by further grouping them into strata (low, medium, high).

In studies reporting no improvement in risk prediction when accounting for renal function, the added value of this variable may be attenuated because it is associated with other risk factors that are already included in $CHADS_2$ and CHA_2DS_2-VASc, such as age and heart failure [27]. In ROCKET AF, traditional stroke risk factors such as age and hypertension were not significantly associated with stroke or SE [4]. Therefore, it may be that renal function is important for predicting stroke in settings where traditional risk factors do not improve prediction. Prior studies have tested the incremental discriminative capacity of novel stroke risk scores among anticoagulated patients to identify patients who are still at high risk of stroke despite taking OAC, with mixed results [4,6,12,13]. As use of OAC in AF expands and the comorbidity burden of patients with AF increases, further work is needed to determine whether readily available, non-traditional risk factors can support identifying patients who have high residual risk despite OAC therapy.

Table 4
% NRI with R_2CHADS_2 at 2 years.

	Overall (n=9743)		OAC (n=7742)		No OAC (n=2301)	
	$CHADS_2$	CHA_2DS_2-VASc	$CHADS_2$	CHA_2DS_2-VASc	$CHADS_2$	CHA_2DS_2-VASc
Original points[1]	0.11 (0.03, 0.18)	0.13 (0.05, 0.19)	0.12 (0.02, 0.18)	0.13 (0.04, 0.22)	0.07 (-0.08, 0.21)	0.13 (0.02, 0.27)
ROCKET AF[2]	0.15 (0.08, 0.22)	0.01 (-0.09, 0.11)	0.13 (0.03, 0.23)	0.01 (-0.11, 0.10)	0.20 (0.04, 0.32)	0.06 (-0.18, 0.22)
<2%, 2-4%, >4%[3]	-0.05 (-0.15, 0.05)	0.01 (-0.08, 0.10)	0.03 (-0.10, 0.14)	0.03 (-0.11, 0.17)	-0.13 (-0.28, -0.04)	-0.11 (-0.24, 0.03)
<2%, >2%[4]	0.0 (-0.08, 0.08)	-0.02 (-0.09, 0.06)	-0.03 (-0.10, 0.05)	-0.07 (-0.15, 0.02)	-0.06 (-0.07, -0.04)	-0.12 (-0.18, -0.05)

[1] Classification based on guidelines and\or original publications: R_2CHADS_2: Low=0-3; Intermediate=4-5; High=6-8; $CHADS_2$: Low=0; Intermediate=1; High=2+; CHA_2DS_2-VASc: Low=0; Intermediate=1; High=2+.
[2] Classification based on ROCKET AF: R_2CHADS_2: Low=0-3; Intermediate=4-5; High=6-8; $CHADS_2$: Low=0-3; Intermediate=4-5; High=6; CHA_2DS_2-VASc: Low=0-4; Intermediate=5-6; High=7-9.
[3] Classification based on common risk thresholds applied to event rates observed in ORBIT-AF: <2%, 2-4%, >4%, corresponded to R_2CHADS_2: Low=0-3; Intermediate=4-5; High=6-8; $CHADS_2$: Low=0-1; Intermediate=2-3; High=4+; CHA_2DS_2-VASc: Low=0-3; Intermediate=4-6; High=7+.
[4] Classification based at the overall ORBIT-AF 2-year event rate (1.83%): corresponded to R_2CHADS_2: Low=0-3; Moderate=4+; $CHADS_2$: Low=0-1; Moderate=2+; CHA_2DS_2-VASc: Low=0-3; Moderate=4+.

4.1. Limitations

Our study has several limitations. First, ORBIT-AF is a voluntary registry, and participating sites may not represent all outpatient AF practices. Second, our assessment of renal function was from a baseline measurement and was not updated longitudinally. Third, the rate of stroke in the ORBIT-AF population is lower than that in other AF populations and may have implications for our power to detect an adjusted association. This is likely due to the high baseline rates of anticoagulation in the cohort, but it may also be explained by differences in the ascertainment of stroke outcomes in a natural practice registry, as opposed to a clinical trial. Therefore, results may differ in populations with higher baseline stroke risk. Fourth, while we found similar results across strata of baseline OAC use, we were unable to examine differences in renal function as a predictor of SSE in patients taking novel OACs, specifically due to the time period for baseline data collection (2010–2011). Patients anticoagulated with non-vitamin K antagonists represent an important population for further study. Finally, observation of a longer follow-up period would draw more specific conclusions concerning the role of renal function in predicting stroke in this study population.

5. Conclusions

In a community patient population with high anticoagulant use in the United States, renal dysfunction did not improve discrimination of traditional embolic risk models. Continued evaluation of potentially novel stroke risk factors in patients with AF is needed, yet methodological differences can yield conflicting results. This underscores the need for future studies evaluating risk scores in AF to be guided by best practices for the assessment of incremental value.

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Appendix A. Supplementary data

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