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ORIGINAL ARTICLE

CHA2DS2-VASc and ATRIA Scores and Clinical Outcomes in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background Heart failure (HF) patients have high risks of thromboembolic events regardless of the category of left ventricular ejection fraction. We sought to assess whether the CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and female sex) and ATRIA (anticoagulation and risk factors in atrial fibrillation) scores could predict clinical outcomes in HF patients with preserved ejection fraction (HFpEF).

Methods We performed a retrospective analysis in a multicenter, America-based population of 1766 HFpEF patients who were stratified according to their baseline CHA2DS2-VASc or ATRIA scores. The CHA2DS2-VASc and ATRIA scores were analyzed as a continuous or categorical variable. The outcomes were stroke, all-cause death, cardiovascular death, any hospitalization, and HF hospitalization.

Results When score was considered as a continuous variable, each point increase in CHA2DS2-VASc was associated with increased risks of stroke (hazard ratio (HR) 1.22, 95% confidence interval (CI) = 1.06–1.41, C-index = 0.62), HF hospitalization (HR 1.08, 95% CI = 1.01–1.17, C-index = 0.59), and any hospitalization (HR 1.06, 95% CI = 1.01–1.11, C-index = 0.57) whereas each point increase in ATRIA was associated with increased risks of stroke (HR 1.11, 95% CI = 1.01–1.21, C-index = 0.62), all-cause death (HR 1.09, 95% CI = 1.05–1.14, C-index = 0.61), cardiovascular death (HR 1.08, 95% CI = 1.02–1.14, C-index = 0.59), HF hospitalization (HR 1.07, 95% CI = 1.03–1.12, C-index = 0.58), and any hospitalization (HR 1.04, 95% CI = 1.01–1.06, C-index = 0.57). When score was regarded as a categorical variable, compared with controls, CHA2DS2-VASc ≥ 4 was associated with increased risks of stroke and hospitalization whereas ATRIA ≥ 8 was associated with increased risks of stroke, death, and hospitalization.

Conclusions The CHA2DS2-VASc and ATRIA scores are associated with risks of adverse outcomes in HFpEF patients. However, the predictive abilities of CHA2DS2-VASc and ATRIA are modest, and their clinical utility in HFpEF remains to be determined.

Clinical trial registration https://clinicaltrials.gov. Identifier: NCT00094302

Keywords Heart failure · Stroke · Adverse outcomes · Risk prediction

Wengen Zhu and Yuzhong Wu are co-authors.

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Introduction

The CHA2DS2-VASc score (congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), and female sex (1 point each), and age ≥ 75 years and prior stroke/transient ischemic attack/thromboembolism (2 points each)) is widely used to predict the risk of stroke in patients with atrial fibrillation (AF) [1, 2]. Current AF guidelines recommend the use of the CHA2DS2-VASc score in the management of antithrombotic therapy [1, 3]. More recently, the application of CHA2DS2-VASc has extended beyond the risk prediction of AF-related stroke. Several studies have shown that CHA2DS2-VASc could predict the risks of stroke [4], death [5], AF [6], or other cardiovascular events [7] in patients with sinus rhythm.

Heart failure (HF) is a highly complex clinical syndrome with a prevalence that increases with age. Several studies have indicated that HF patients have a high risk of stroke and systemic embolism regardless of the presence of AF [8–10]. HF is an independent risk factor of stroke in AF and thus incorporated into the CHA2DS2-VASc score. Recent researches have indicated that CHA2DS2-VASc seemingly could identify the risk of stroke in HF patients with or without AF [11, 12], but these studies included both HF patients with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF) [13] or only included the HFrEF population [14]. However, the predictive accuracy of the CHA2DS2-VASc score for stratifying the risks of adverse outcomes in HFpEF patients has not yet been determined. Since previous studies indicated that the CHA2DS2-VASc score only modestly predicted adverse events in HF patients, there is a need to examine if other scoring strategies will be beneficial for stratifying adverse outcomes in HF patients. Most of the components in the ATRIA (anticoagulation and risk factors in atrial fibrillation) score are included in the CHA2DS2-VASc score. A prior meta-analysis suggests that ATRIA has a better predictive ability for stroke than CHA2DS2-VASc in patients with AF [15]. However, there is a dearth of study to determine the performance of the ATRIA score in patients with HF. Herein, based on the data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial, we performed a post hoc analysis to assess whether the CHA2DS2-VASc and ATRIA scores could predict clinical outcomes in patients with HFpEF.

Methods

Subjects and Study Protocol

The TOPCAT trial, a phase III, randomized, double-blind, placebo-controlled study, was designed to test the clinical benefits of spironolactone treatment in patients with symptomatic HFpEF with a mean follow-up of 3.3 years [16]. The study protocol was approved by the institutional review board at each of the participating sites. Eligible participants had an age of ≥ 50 years, a left ventricular ejection fraction (LVEF) of ≥ 45%, and a serum potassium level of < 5.0 mmol/l. In addition, patients should have a history of HF hospitalization within 12 months or an elevated brain natriuretic peptide within 60 days (B-type natriuretic peptide level of ≥ 100 pg/ml or N-terminal pro–B-type natriuretic peptide of ≥ 360 pg/ml). All relevant data were obtained from the National Heart, Lung, and Blood Institute by applying to the Biologic Specimen and Data Repository Information Coordinating Center.

Risk Stratification Using CHA2DS2-VASc and ATRIA

A total of 3445 patients were enrolled from six countries including the Americas (USA, Canada, Argentina, and Brazil), Russia, and Georgia. All patients signed an informed consent form. Due to concerns about the representativeness of patients in Russia and Georgia [17], only participants from the Americas (n = 1767) were included in this study [18, 19]. After excluding patients with missing data, we included 1766 and 1752 patients to calculate the baseline CHA2DS2-VASc and ATRIA scores, respectively (Supplemental Table 1). These patients were classified into two groups according to the median CHA2DS2-VASc (CHA2DS2-VASc ≥ 4 and CHA2DS2-VASc < 4) or ATRIA (ATRIA ≥ 8 and ATRIA < 8) scores.

Patient Follow-Up

Follow-up visits to monitor symptoms, medications, and events and to dispense study drug were scheduled every 4 months during the subject's first year on the study and every 6 months thereafter. Data on participants who did not have an event of time-to-event outcomes were censored at the date of last available follow-up information for clinical events.

Outcomes and Its Definitions

The outcomes of interest in this study were stroke, all-cause death, cardiovascular death, any hospitalization, and HF hospitalization. These outcomes were centrally adjudicated by a blinded clinical endpoint committee at Brigham and Women's Hospital. The detailed definitions of outcomes were previously described [16].

Statistical Analysis

For the baseline patient characteristics, continuous variables were presented as the mean ± standard deviation or median

Table 1 Clinical characteristics of HFpEF patients classified by the median CHA2DS2-VASc or ATRIA scores

	CHA2DS2-VASc < 4 (*n* = 411)	CHA2DS2-VASc ≥ 4 (*n* = 1355)	*P* value	ATRIA < 8 (*n* = 861)	ATRIA ≥ 8 (*n* = 891)	*P* value
Randomization, *n*						
Spironolactone	208 (50.6)	678 (50.0)	0.88	427 (49.6)	451 (50.6)	0.70
Age						
Age, years	62.9 ± 7.7	74.1 ± 8.7	< 0.001	64.8 ± 7.2	78.1 ± 7.0	< 0.001
Age ≥ 75 years, *n*	23 (5.6)	724 (53.4)	< 0.001	45 (5.2)	699 (78.5)	< 0.001
Female, *n*	98 (23.8)	784 (57.9)	< 0.001	346 (40.2)	529 (59.4)	< 0.001
White race, *n*	311 (75.7)	1072 (79.1)	0.16	652 (75.7)	723 (81.1)	0.007
Heart rate, beats/min	70 (62–78)	68 (61–76)	0.09	68 (61–77)	68 (60–75)	0.09
SBP, mmHg	125 (114–137)	130 (118–139)	0.001	128 (117–138)	129 (118–139)	0.27
DBP, mmHg	74 (65–80)	70 (62–80)	< 0.001	73 (64–80)	70 (60–80)	< 0.001
BMI, kg/m^2	33.6 (28.5–39.5)	32.6 (27.8–38.1)	0.043	34.4 (29.5–40.8)	31.2 (26.8–36.1)	< 0.001
Waist Circumference, cm	111.8 (98.0–124.5)	108 (96.5–119.4)	0.001	111.8 (100.0–126.0)	106.7 (95.0–116.8)	< 0.001
Smoking status, *n*			< 0.001			< 0.001
Current smoking	49 (11.9)	68 (5.0)		90 (10.5)	27 (3.0)	
Ever smoking	215 (52.3)	684 (50.5)		455 (52.8)	436 (48.9)	
Never smoking	147 (35.8)	603 (44.5)		316 (36.7)	428 (48.0)	
QRS duration, ms	92 (82–108)	94 (80–106)	0.91	92 (82–106)	94 (80–106)	0.99
NYHA functional class, *n*						
III and IV	112 (27.3)	509 (37.6)	< 0.001	266 (30.9)	345 (38.7)	< 0.001
Laboratory values						
Hemoglobin, mg/dl	13.5 (12.2–14.6)	12.7 (11.6–13.8)	< 0.001	13.1 (12.0–14.3)	12.5 (11.5–13.7)	< 0.001
Hematocrit, %	40.0 (37.0–43.1)	38.0 (35.0–41.1)	< 0.001	39.3 (36.2–42.8)	38.0 (35.0–41.0)	< 0.001
WBC, k/μl	7.0 (5.9–8.4)	7.1 (5.9–8.5)	0.64	7.2 (5.9–8.7)	7.0 (5.8–8.4)	0.028
PLT, k/μl	218 (181–262.5)	219 (182–266)	0.52	225 (184–271)	215 (180–260)	0.019
Serum Na^+, mg/dl	140 (138–142)	140 (138–142)	0.23	140 (138–142)	140 (138–142)	0.25
Serum K^+, mg/dl	4.2 (3.9–4.5)	4.2 (3.9–4.5)	0.58	4.2 (3.9–4.5)	4.2 (3.9–4.5)	0.83
ALT, U/l	24 (17–33)	21 (15–30)	< 0.001	23 (16–33)	21 (15–30)	< 0.001
AST, U/l	24 (19–30)	22 (18–29)	< 0.001	23 (18–29)	22 (18–29)	0.09
ALP, U/l	84 (67–110.5)	83 (66–113)	0.60	85 (68–112)	83 (64–111.5)	0.08
Serum creatinine, mg/dl	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.08	1.1 (0.9–1.3)	1.2 (0.9–1.4)	< 0.001
eGFR, ml/(min*1.73m^2)	69.9 (57.8–87.8)	58.0 (47.6–73.9)	< 0.001	66.6 (54.8–82.8)	56.2 (44.1–71.0)	< 0.001
Comorbidities, *n* (%)						
Previous HF hospitalization	265 (64.5)	776 (57.3)	0.011	546 (63.4)	484 (54.3)	< 0.001
Previous stroke	1 (0.2)	157 (11.6)	< 0.001	0 (0.0)	157 (17.6)	< 0.001
Previous MI	22 (5.4)	338 (24.9)	< 0.001	168 (19.5)	191 (21.4)	0.35
CABG	47 (11.4)	290 (21.4)	< 0.001	160 (18.6)	176 (19.8)	0.58
PCI	41 (10.0)	304 (22.4)	< 0.001	169 (19.6)	176 (19.8)	0.99
PAD	12 (2.9)	195 (14.4)	< 0.001	89 (10.3)	117 (13.1)	0.08
Dyslipidemia	237 (57.7)	1014 (74.8)	< 0.001	591 (68.6)	651 (73.1)	0.047
Hypertension	304 (74.0)	1285 (94.8)	< 0.001	753 (87.5)	824 (92.5)	0.001
Atrial fibrillation	149 (36.3)	594 (43.8)	0.008	308 (35.8)	431 (48.4)	< 0.001
COPD	66 (16.1)	225 (16.6)	0.85	153 (17.8)	135 (15.2)	0.16
Asthma	45 (10.9)	149 (11.0)	1.00	102 (11.8)	91 (10.2)	0.31
Diabetes mellitus	111 (27.0)	678 (50.0)	< 0.001	391 (45.4)	392 (44.0)	0.59
Thyroid diseases	53 (12.9)	280 (20.7)	0.001	124 (14.4)	208 (23.3)	< 0.001
Medications						
ACE-I or ARB	328 (79.8)	1068 (78.8)	0.72	708 (82.2)	676 (75.9)	0.001
Beta-blocker	318 (77.4)	1070 (79.0)	0.53	699 (81.2)	675 (75.8)	0.007

Table 1 (continued)

	CHA2DS2-VASc < 4 (n = 411)	CHA2DS2-VASc ≥ 4 (n = 1355)	P value	ATRIA < 8 (n = 861)	ATRIA ≥ 8 (n = 891)	P value
Calcium channel blocker	135 (32.8)	547 (40.4)	0.007	308 (35.8)	368 (41.3)	0.020
Diuretic	356 (86.6)	1218 (89.9)	0.08	754 (87.6)	806 (90.5)	0.06
Long acting nitrate	48 (11.7)	257 (19.0)	0.001	134 (15.6)	167 (18.7)	0.09
Statin	231 (56.2)	917 (67.7)	< 0.001	561 (65.2)	579 (65.0)	0.98
Antiplatelets	244 (59.4)	832 (61.4)	0.50	548 (63.6)	521 (58.5)	0.030
Anticoagulants	130 (31.6)	482 (35.6)	0.16	264 (30.7)	345 (38.7)	< 0.001

Values are n (%), mean ± SD, or median (25th, 75th quartiles)

SBP systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *WBC* white blood cell count, *PLT* platelet count, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *ALP* alkaline phosphatase, *HF* heart failure, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *PAD* peripheral arterial disease, *COPD* chronic obstructive pulmonary disease, *ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

with interquartile using unpaired Student's t tests (Gaussian distribution) or Wilcoxon-Mann-Whitney tests (non-Gaussian distribution) whereas categorical variables were expressed as proportions using the χ^2 tests. The incidence of stroke was described with incidence rates per 100 person-years and estimated cumulative incidence at different time-points in the competing risk models (Fine and Gray models). The CHA2DS2-VASc and ATRIA scores were analyzed as a continuous or categorical variable, separately, when their association with adverse outcomes was assessed. The effect estimates of this study were hazard ratios (HRs) and its confidence interval (CIs). The HRs of outcomes not related to death (stroke, HF hospitalization, and any hospitalization) were derived from the competing risk models whereas those of the death-related outcomes (all-cause death and cardiovascular death) were derived from the Cox proportional hazards models. In addition, C-indexes were calculated to determine the discriminatory properties of the CHA2DS2-VASc and ATRIA scores.

The statistical analyses were performed using R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), with packages of tableone, mice, survival, survminer, cmprsk, and timeROC. A two-tailed P value of < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Eligible participants were divided into the following groups: CHA2DS2-VASc < 4 (n = 411) and CHA2DS2-VASc ≥ 4 (n = 1355), or ATRIA < 8 (n = 861) and ATRIA ≥ 8 (n = 891). As shown in Table 1, compared with controls, patients with CHA2DS2-VASc ≥ 4 or ATRIA ≥ 8 were older; were predominantly female; had lower diastolic blood pressure, body mass index, waist circumference, and estimated glomerular filtration rate; and were less likely to be current smokers. Patients with CHA2DS2-VASc ≥ 4 or ATRIA ≥ 8 were more likely to be New York Heart Association functional class III/IV, had a greater proportion of age ≥ 75 years, and had more comorbidities and prescription medications. The distributions of the CHA2DS2-VASc and ATRIA scores in HFpEF patients are shown in Supplemental Figure 1. Nearly 87.1% of patients scored 3 to 6 points in the CHA2DS2-VASc score whereas 56.3% of patients scored 7 to 10 points in the ATRIA score.

Incidence of Stroke in HFpEF Patients

The median follow-up duration was 2.8 years (interquartile range, 1.7–4.1). A total of 4.4% of patients (77/1766) had an event of stroke. The incidence of stroke in HFpEF patients gradually increased across the CHA2DS2-VASc score (Supplemental Table 2). The average incidence of stroke was 1.5 (95% CI = 1.2–1.8) per 100 patient-years. The estimated cumulative incidence of stroke at 1, 2, 3, 4, and 5 years in the competing risk models was 1.7%, 2.7%, 3.6%, 5.2%, and 6.2%, respectively. In addition, the incidence of stroke was 1.8 (95% CI = 1.2–2.3) per 100 patient-years in patients with AF and 1.8 (95% CI = 1.2–2.3) and 1.3 (95% CI = 0.9–1.7) per 100 patient-years in patients without AF (Supplemental Table 3).

Association of the CHA2DS2-VASc Score with Outcomes

The associations of each individual component in the CHA2DS2-VASc score with outcomes are shown in Supplemental Table 1. When score was analyzed as a continuous variable, every 1-point increase in CHA2DS2-VASc was associated with increased risks of stroke (HR 1.22, 95% CI =

1.06–1.41), HF hospitalization (HR 1.08, 95% CI = 1.01–1.17), and any hospitalization (HR 1.06, 95% CI = 1.01–1.11) after adjusting for the confounders (Table 2). When CHA2DS2-VASc was analyzed as a categorical variable, we observed a low number of stroke (nine events) in patients with a CHA2DS2-VASc score of < 4. Compared with patients with CHA2DS2-VASc < 4, those with CHA2DS2-VASc ≥ 4 had higher risks of stroke (HR 2.35, 95% CI = 1.16–4.77), HF hospitalization (HR 1.41, 95% CI = 1.07–1.86), and any hospitalization (HR 1.17, 95% CI = 1.00–1.36) (Fig. 1 and Table 2). Similar results were observed after we excluded patients with AF (Supplemental Table 4).

Association of the ATRIA Score with Outcomes

The associations between each individual component of the ATRIA score and the risk of outcomes are shown in Supplemental Table 1. When ATRIA was regarded as a continuous variable, every 1-point increase in ATRIA was associated with increased risks of stroke (HR 1.11, 95% CI =

Table 2 Associations of the CHA2DS2-VASc score with outcomes in HFpEF patients

	Events, *n* (%)	Person-years	Incidence rates, per 100 person-years	Hazard ratios (95% CIs)				C-indexes
				Crude	*P* value	Adjusted[c]	*P* value	
Stroke[a]								
CHA2DS2-VASc < 4	9 (2.2)	1180	0.8 (0.4–1.5)	Ref.	–	Ref.	–	
CHA2DS2-VASc ≥ 4	68 (5.0)	3961	1.7 (1.4–2.2)	2.20 (1.10–4.42)	0.026	2.35 (1.16–4.77)	0.018	
Overall[b]	77 (4.4)	5141	1.5 (1.2–1.9)	1.18 (1.03–1.35)	0.016	1.22 (1.06–1.41)	0.006	0.62 (0.54–0.70)
All-cause death								
CHA2DS2-VASc < 4	64 (15.6)	1195	5.4 (4.2–6.8)	Ref.	–	Ref.	–	
CHA2DS2-VASc ≥ 4	323 (23.8)	4071	7.9 (7.1–8.8)	1.47 (1.12–1.92)	0.005	1.27 (0.96–1.67)	0.10	
Overall[b]	387 (21.9)	5266	7.3 (6.7–8.0)	1.12 (1.04–1.20)	0.002	1.05 (0.98–1.14)	0.18	0.58 (0.53–0.63)
Cardiovascular death								
CHA2DS2-VASc < 4	43 (10.5)	1195	3.6 (2.7–4.8)	Ref.	–	Ref.	–	
CHA2DS2-VASc ≥ 4	180 (13.3)	4071	4.4 (3.8–5.1)	1.22 (0.87–1.70)	0.25	1.06 (0.75–1.49)	0.75	
Overall[b]	223 (12.6)	5266	4.2 (3.7–4.8)	1.09 (0.99–1.20)	0.08	1.04 (0.93–1.15)	0.51	0.56 (0.50–0.62)
Any hospitalization[a]								
CHA2DS2-VASc < 4	223 (54.3)	779	28.6 (25.6–32.0)	Ref.	–	Ref.	–	
CHA2DS2-VASc ≥ 4	839 (61.9)	2349	35.7 (33.8–37.7)	1.23 (1.07–1.43)	0.005	1.17 (1.00–1.36)	0.048	
Overall[b]	1062 (60.1)	3128	33.9 (32.3–35.6)	1.08 (1.04–1.13)	< 0.001	1.06 (1.01–1.11)	0.016	0.57 (0.50–0.64)
HF Hospitalization[a]								
CHA2DS2-VASc < 4	67 (16.3)	1100	6.1 (4.6–7.5)	Ref.		Ref.	–	
CHA2DS2-VASc ≥ 4	333 (24.6)	3494	9.5 (8.5–10.6)	1.53 (1.18–1.98)	0.002	1.41 (1.07–1.86)	0.014	
Overall[b]	400 (22.7)	4594	8.7 (6.9–9.6)	1.13 (1.05–1.20)	0.001	1.08 (1.01–1.17)	0.033	0.59 (0.54–0.64)

HFpEF heart failure patients with preserved ejection fraction, *HF* heart failure, *CI* confidence interval

[a] Using competing risks regression

[b] CHA2DS2-VASc scores were used as continuous variable to derive hazard ratios

[c] Adjusted for race, waist circumference, smoking status, heart rate, diastolic blood pressure, estimated glomerular filtration rate, chronic obstructive pulmonary disease, atrial fibrillation, antiplatelets, and anticoagulants

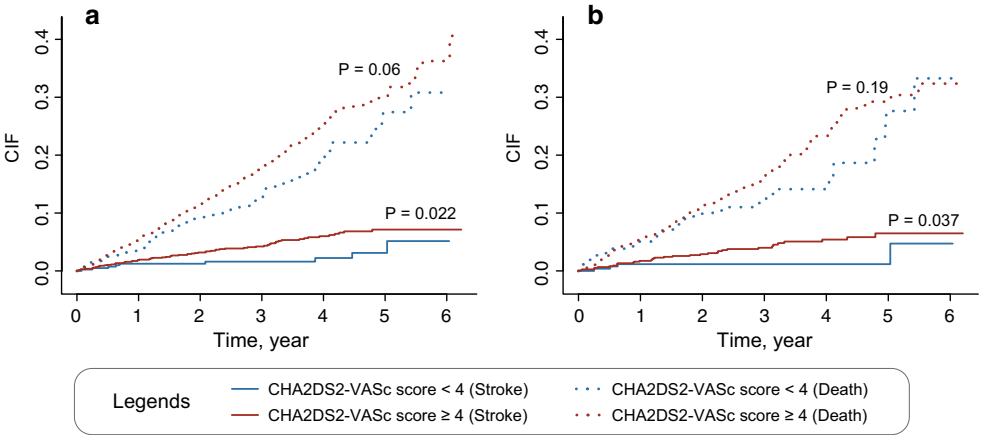

Fig. 1 Cumulative incidence curves of stroke in HFpEF patients (A, entire patients; B, patients without AF) according to the CHA2DS2-VASc score. *HFpEF* heart failure patients with preserved ejection fraction, *AF* atrial fibrillation, *CIF* cumulative incidence function

1.01–1.21), all-cause death (HR 1.09, 95% CI = 1.05–1.14), cardiovascular death (HR 1.08, 95% CI = 1.02–1.14), HF hospitalization (HR 1.07, 95% CI = 1.03–1.12), and any hospitalization (HR 1.04, 95% CI = 1.01–1.06) after the multivariate adjustment (Table 3). When ATRIA was analyzed as a categorical variable, compared with controls, patients with ATRIA ≥ 8 had greater risks of stroke (HR 1.89, 95% CI = 1.18–3.05), all-cause death (HR 1.64, 95% CI = 1.32–2.04), cardiovascular death (HR 1.47, 95% CI = 1.10–1.95), HF hospitalization (HR 1.32, 95% CI = 1.07–1.64), and any hospitalization (HR 1.26, 95% CI = 1.11–1.43) (Fig. 2 and Table 3). Similar results were observed after we excluded patients with AF (Supplemental Table 5).

Predictive Ability of the CHA2DS2-VASc and ATRIA Scores

The C-indexes for the predictive ability of CHA2DS2-VASc score are 0.62 (95% CI = 0.54–0.70) in stroke, 0.58 (95% CI = 0.53–0.63) in all-cause death, 0.56 (95% CI = 0.50–0.62) in cardiovascular death, 0.57 (95% CI = 0.50–0.64) in any hospitalization, and 0.59 (95% CI = 0.54–0.64) in HF hospitalization (Table 2). The C-indexes for the predictive ability of ATRIA score are 0.62 (95% CI = 0.54–0.70) in stroke, 0.61 (95% CI = 0.56–0.66) in all-cause death, 0.59 (95% CI = 0.53–0.65) in cardiovascular death, 0.57 (95% CI = 0.51–0.63) in any hospitalization, and 0.58 (95% CI = 0.53–0.63) in HF hospitalization (Table 3).

Discussion

Principal Findings

In HFpEF patients, our current study based on a retrospective analysis of the TOPCAT trial suggested that (i) the incidence of stroke was 1.5 per 100 patient-years; (ii) every 1-point increase in the CHA2DS2-VASc score was associated with increased risks of stroke and hospitalization whereas each point increase in the ATRIA score was related with increased risks of stroke, hospitalization, and death; (iii) patients with higher CHA2DS2-VASc or ATRIA scores had higher incidence rates of adverse outcomes; and (iv) the CHA2DS2-VASc and ATRIA scores had modest abilities for predicting the development of adverse outcomes.

Comparison with Other Studies

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), HF patients with a lower level of LVEF have a higher risk of thromboembolism [20]. Siller-Matula and co-workers [21] detected an inverse association of LVEF with thromboembolic events in AF patients, suggesting that the incidence of thromboembolism in patients with HFpEF was lower than that in the non-HFpEF population. In contrast, other studies indicated that the incidence rates of thromboembolic complications and death in HFpEF were similar (or even higher) to those in HFrEF [10, 11, 22]. Based on our data of the TOPCAT trial, the average incidence rate of stroke was 1.5 per 100 patient-years in HFpEF patients. Consistent with data from the CHARM-Preserved and I-Preserve trials [23], we found that the incidence rates were 1.8 and 1.3 per 100 patient-years in patients with and without AF, respectively.

HF patients without AF have a high risk of stroke or death [24, 25]. The causative role of HFpEF in the pathophysiology of stroke is independent of AF [26]. HFpEF could lead to AF development mediated by atrial myopathy whereas AF is likely a marker of more advanced inflammatory and fibrotic atrial conditions [26]. However, AF is unable to directly explain stroke risk in HFpEF [26]. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, a combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin could reduce the risks of major cardiovascular events compared with the single use of aspirin in patients with stable coronary artery disease and sinus rhythm [27]. Data from the Cardiovascular Outcome Modification,

Table 3 Associations of the ATRIA score with outcomes in HFpEF patients

	Events, *n* (%)	Person-years	Incidence rates, per 100 person-years	Hazard ratios (95% CIs)				C-indexes
				Crude	*P* value	Adjusted[c]	*P* value	
Stroke[a]								
ATRIA < 8	27 (3.1)	2529	1.1 (0.7–1.5)	Ref.	–	Ref.	–	
ATRIA ≥ 8	50 (5.6)	2578	1.9 (1.4–2.5)	1.74 (1.09–2.77)	0.021	1.89 (1.18–3.05)	0.009	
Overall[b]	77 (4.4)	5107	1.5 (1.2–1.8)	1.09 (1.00–1.19)	0.06	1.11 (1.01–1.21)	0.032	0.62 (0.54–0.70)
All-cause death								
ATRIA < 8	143 (16.6)	2575	5.6 (4.6–6.5)	Ref.	–	Ref.	–	
ATRIA ≥ 8	242 (27.2)	2657	9.1 (8.0–10.3)	1.64 (1.34–2.02)	< 0.001	1.64 (1.32–2.04)	< 0.001	
Overall[b]	385 (22.0)	5232	7.4 (6.6–8.1)	1.10 (1.05–1.14)	< 0.001	1.09 (1.05–1.14)	< 0.001	0.61 (0.56–0.66)
Cardiovascular death								
ATRIA < 8	88 (10.2)	2575	3.4 (2.7–4.1)	Ref.	–	Ref.	–	
ATRIA ≥ 8	133 (14.9)	2657	5.0 (4.2–5.9)	1.47 (1.12–1.92)	0.006	1.47 (1.10–1.95)	0.008	
Overall[b]	221 (12.6)	5232	4.2 (3.7–4.8)	1.08 (1.03–1.14)	0.003	1.08 (1.02–1.14)	0.005	0.59 (0.53–0.65)
Any hospitalization[a]								
ATRIA < 8	485 (56.3)	1606	30.2 (27.5–32.9)	Ref.	–	Ref.	–	
ATRIA ≥ 8	570 (64.0)	1506	37.8 (34.7–41.0)	1.22 (1.08–1.38)	0.001	1.26 (1.11–1.43)	< 0.001	
Overall[b]	1055 (60.2)	3112	33.9 (31.9–35.9)	1.03 (1.01–1.06)	0.008	1.04 (1.01–1.06)	0.008	0.57 (0.51–0.63)
HF hospitalization[a]								
ATRIA < 8	172 (20.0)	2289	7.5 (6.4–8.6)	Ref.	–	Ref.	–	
ATRIA ≥ 8	224 (25.1)	2279	9.8 (8.5–11.1)	1.25 (1.03–1.53)	0.026	1.32 (1.07–1.64)	0.009	
Overall[b]	396 (22.6)	4568	8.7 (7.8–9.5)	1.06 (1.02–1.11)	0.004	1.07 (1.03–1.12)	0.001	0.58 (0.53–0.63)

HFpEF heart failure patients with preserved ejection fraction, *HF* heart failure, *CI* confidence interval

[a] Using competing risks regression

[b] ATRIA scores were used as continuous variable to derive hazard ratios

[c] Adjusted for race, waist circumference, smoking status, heart rate, diastolic blood pressure, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, antiplatelets, and anticoagulants.

Measurement, and Evaluation of Rivaroxaban in Patients with Heart Failure (COMMANDER-HF) trial suggest a reduced stroke risk in HF patients without AF treated with a low dose of rivaroxaban [28]. Oral anticoagulation therapy (OAT) might exert a protective effect against stroke conferred by HF [10] but introduce a high risk of bleeding [29]. Nevertheless, OAT-related reductions in thromboembolic events further demonstrate the established role of HF in developing stroke.

Prior researches shown in Supplemental Table 6 have verified the role of CHA2DS2-VASc in risk prediction among HF patients from different settings, such as the general population [25], hospitalized patients for new-onset or prevalent HF [12, 30, 31], discharged HF patients [24], patients candidate for cardiac resynchronization therapy [32], and acute decompensated HF patients [11]. The CHA2DS2-VASc score was found to have only modest predictive capacity for death and stroke in HFrEF patients. Since a mix of HFpEF and HFrEF patients or only the HFrEF population was included in these initial studies, the direct clinical utility of CHA2DS2-VASc in risk stratification in patients with HFpEF remains unclear. To our knowledge, we first found the CHA2DS2-

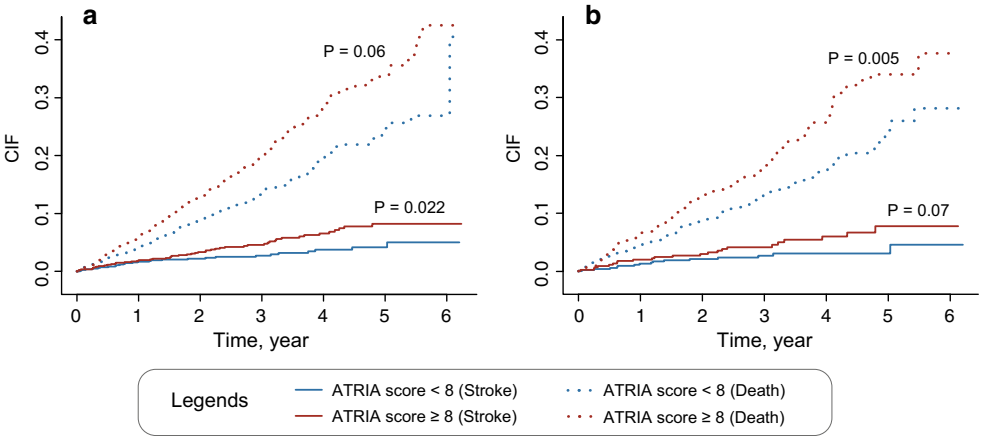

Fig. 2 Cumulative incidence curves of stroke in HFpEF patients (A, entire patients; B, patients without AF) according to the ATRIA score. *HFpEF* heart failure patients with preserved ejection fraction, *AF* atrial fibrillation, *CIF* cumulative incidence function

VASc score could predict cardiovascular outcomes in chronic patients with HFpEF. Consistent with the previous findings in HFrEF, the CHA2DS2-VASc score had a modest diagnostic accuracy for adverse events in HFpEF patients. A prior meta-analysis by Zhu et al. [15] has suggested that the CHA2DS2-VASc score significantly outperformed the ATRIA score in predicting stroke in AF patients. In this study, we first demonstrated that the ATRIA score as a continuous variable could help stratify adverse outcomes among HF patients with a modest predictive ability.

Implications and Further Research

HF patients have high risks of mortality and morbidity. It is necessary to develop a simple and practical risk assessment score to identify high-risk patients with HF and optimize therapeutic approaches to reduce adverse outcomes. Although previous studies have indicated the potential usefulness of the CHA2DS2-VASc score, its direct clinical utility in risk stratification in patients with HF remains unclear. Our current data indicated that the ATRIA or CHA2DS2-VASc scores seemingly could be used for risk stratification in HFpEF patients, but their predictive abilities were modest. The unimpressive C-indexes might be attributed to inherent limitations in the ability of ATRIA or CHA2DS2-VASc to discriminate between patients with HF who will and will not develop adverse outcomes. Therefore, future studies are needed to confirm our findings and evaluate the ability of modified CHA2DS2-VASc or ATRIA scores to predict adverse outcomes in HFpEF patients.

Strengths and Limitations of the Study

To our knowledge, this was the first study to evaluate the performances of ATRIA and CHA2DS2-VASc scores to predict adverse outcomes in patients with HFpEF. Another strength of this study was that we accounted for the competing risk of death, an important issue when investigating the predictive ability of risk models in HF patients with a high death rate. Nevertheless, we should acknowledge several limitations. First, the data of this retrospective study were based on a post hoc, not pre-specified, analysis of a randomized controlled trial. It is possible that healthier patients were selected and the unmeasured confounders were not noted, which might influence the validity and generalizability of our findings. Second, as mentioned previously, the outcomes of this study were the secondary endpoints, and the specified subtypes of stroke were not assessed in the TOPCAT trial. Third, the subgroup analysis based on patients with or without AF was not performed due to the limiting sample size. Instead, we excluded AF patients in the sensitivity analysis. Finally, the records for some indexes of the CHA2DS2-VASc or ATRIA scores were incomplete in the TOPCAT trial, which might underscore the total points of these two scores. For example, the TOPCAT trial provided the data of prior stroke, but other thromboembolic events were unavailable.

Conclusions

Based on data from the TOPCAT trial, the CHA2DS2-VASc and ATRIA scores could predict the risks of clinical outcomes in patients with HFpEF. Both of the CHA2DS2-VASc and ATRIA scores had modest predictive abilities for adverse outcomes in patients with HFpEF. Future studies are needed to determine the clinical utility of these scores in patients with HFpEF.

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Author Contribution Under the directions of Yugang Dong and Chen Liu, Yuzhong Wu and Wengen Zhu performed the study design, data extraction, and statistical analysis. Wengen Zhu and Yuzhong Wu wrote the original draft while Chen Liu revised the draft. All other authors

helped check the data to ensure accuracy and edit the manuscript prior to submission to ensure the standard English grammar.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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