ORIGINAL RESEARCH ARTICLE

Usefulness of CHADS2, R2CHADS2, and CHA2DS2-VASc scores for predicting incident atrial fibrillation in heart failure with preserved ejection fraction patients

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Abstract

Aims Coexisting of atrial fibrillation (AF) in patients with heart failure with preserved ejection fraction (HFpEF) could increase the risk of mortality. In this study, we aimed to assess the values of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores for AF prediction in HFpEF patients.

Methods and results We performed a retrospective analysis on symptomatic HFpEF patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial. Associations of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores with the risk of incident AF in HFpEF patients without baseline AF (*n* = 2202) were assessed using the multivariable competing risk regression models. The discriminatory performances of these scores were calculated using the C-index. During a median follow-up of 3.3 years, the average incidence of AF was 1.80 per 100 patient-years in HFpEF patients. When score was analysed as a continuous variable, per 1-point increase in the CHADS2 (hazard ratio [HR] = 1.42, 95% confidence interval [CI]: 1.20–1.68, C-index: 0.71), R2CHADS2 (HR = 1.25, 95% CI: 1.10–1.42, C-index: 0.69), or CHA2DS2-VASc (HR = 1.30, 95% CI: 1.16–1.46, C-index: 0.70) scores was associated with an increased risk of incident AF. When score was analysed as a categorical variable, patients with CHADS2 ≥ 3 (HR = 2.62, 95% CI: 1.70–4.04), R2CHADS2 ≥ 3 (HR = 2.55, 95% CI: 1.56–4.17), or CHA2DS2-VASc ≥ 4 (HR = 2.54, 95% CI: 1.59–4.07) had a higher risk of incident AF compared with the corresponding controls.

Conclusions Our data first suggest that the CHADS2, R2CHADS2, and CHA2DS2-VASc scores could predict the risk of incident AF in HFpEF patients with modest predictive abilities.

Introduction

Heart failure (HF) is a highly complex clinical syndrome with a high prevalence that increases with age, including patients with HF with reduced ejection fraction (HFrEF) and those with preserved ejection fraction (HFpEF). HFpEF, a highly heterogeneous phenotype, and AF share common risk factors and often coexist.[1,2] In addition to that HF is associated with a higher incidence rate of atrial fibrillation (AF), several studies have indicated that patients with HFpEF are at a greater risk for AF than those with HFrEF in acute or chronic settings.[3–6] Current evidence on prognostic implications of AF in HF patients suggest that AF at baseline or new-onset AF during the follow-up is associated with an increased risk of mortality in patients with HFpEF.[3,7–9] Early identification of AF in patients with HFpEF may prompt the initiation

of treatments to improve prognosis. Currently, the specific screening strategies such as scoring systems for predicting AF in patients with HFpEF have not yet been determined.

The CHADS2 (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus [1 point each], and prior stroke/transient ischaemic attack/thromboembolism [doubled]) and CHA2DS2-VASc (congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], and female [1 point each], and age ≥75 years and prior stroke/transient ischaemic attack/thromboembolism [doubled]) scores are the two most widely used models to predict embolic risks in patients with AF.[10] The R2CHADS2 score, established by adding creatinine clearance (doubled) into the CHADS2 score, seemingly could improve the predictive ability of stroke in patients with AF.[11] In recent years, several studies have suggested that CHADS2, R2CHADS2, and CHA2DS2-VASc could predict new occurrence of AF in the general population,[12–15] patients after AF ablation,[16] or patients with acute coronary syndrome.[17,18] In addition, the individual components in these scores are also the potential risk factors of AF in HF patients. Therefore, it would be interesting to determine if the CHADS2, R2CHADS2, and CHA2DS2-VASc scores could predict AF in HFpEF patients. Based on data of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, we aimed to assess the values of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores for AF prediction among patients with HFpEF.

Methods

Study population

The TOPCAT trial was a phase III, multicentred, international, randomized, double-blind, and placebo-controlled study, which evaluated the effectiveness of spironolactone in reducing cardiovascular events in patients with symptomatic HFpEF with a mean follow-up of 3.3 years.[19] A total of 3445 patients with an age of ≥50 years, a left ventricular ejection fraction (LVEF) of ≥45%, a serum potassium level of <5.0 mmol/L, and a history of HF hospitalization within the previous 12 months or elevated brain natriuretic peptide level within 60 days before randomization were enrolled. Exclusion criteria included severe systemic illness with a life expectancy of less than 3 years, severe renal dysfunction, and specific coexisting conditions. The institutional review board at each of the participating sites approved the study. All participants signed consent forms. The data access was granted by the National Heart, Lung, and Blood Institute, via the Biologic Specimen and Data Repository Information Coordinating Center.

Risk stratification using CHADS2, R2CHADS2, and CHA2DS2-VASc scores

Variables of demographic and clinical characteristics at baseline were retrieved from the dataset for calculating the CHADS2, R2CHADS2, and CHA2DS2-VASc scores. There were a total of nine individual components among the three studied scores, including congestive heart failure (1 point), hypertension (1 point), age category (1 point for age ≥75 years in CHADS2 and R2CHADS2; 1 point for age 65–74, 2 points for age ≥75 years in CHA2DS2-VASc), diabetes mellitus (1 point), prior stroke (doubled), vascular diseases (1 point, only applicable to CHA2DS2-VASc), female sex (1 point, only applicable to CHA2DS2-VASc) and renal dysfunction (doubled, only applicable to R2CHADS2).

In the CHADS2, R2CHADS2, and CHA2DS2-VASc scores, one shared component was 'congestive heart failure' defined as HF patients with moderate-to-severe left ventricular dysfunction or acute decompensated HF regardless of LVEF category. Therefore, each HFpEF patient was scored at least 1 point in our study. Renal dysfunction was defined as an estimated glomerular filtration rate of less than 60 mL/(min*1.73 m^2). The remaining risk factors were determined based on a combination of medical record review and interview at baseline visits.

Follow-up information and outcome

Participants were followed up every 4 months during their first year on the study, and every 6 months thereafter, to monitor incident AF. The events of incident AF were adjudicated by 12-lead electrocardiogram (ECG) at enrolment or available medical documentation.[20] 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.

Statistical analysis

For the baseline characteristics, the continuous variables were expressed as the mean ± standard deviation or median with interquartile range using the unpaired Student's *t*-tests (Gaussian distribution) or Wilcoxon–Mann–Whitney tests (non-Gaussian distribution), whereas categorical variables were presented as proportions using the χ^2 tests. The incidence of AF in the follow-up was described with an incidence rate per 100 person-years. The CHADS2, R2CHADS2, and CHA2DS2-VASc scores were separately analysed as a continuous variable (per 1-point increase) or categorical variable (split by the median of scores), when their associations with incident AF were assessed. The cumulative incidence curves of incident AF were also plotted when the scores were

analysed as a categorical variable. The associations of individual components in each score with incident AF were estimated in the competing risk models (Fine and Grey models). The effect estimates of this study were hazard ratios (HRs) and confidence intervals (CIs), which were derived from the competing risk models.

To determine the discriminatory performances of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores, the C-indexes were calculated by using the receiver operating characteristics (ROC) curves. We compared the performances of two scores by calculating the Z-statistic as follows: A_{Z1} and A_{Z2} represent C-indexes of the corresponding risk scores and SE represents the corresponding standard errors.

$$Z = \frac{A_{Z1} - A_{Z2}}{\sqrt{SE_1^2 + SE_2^2}}.$$

The statistical analyses were performed using R software version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria), with packages of *tableone*, *cmprsk*, *survival*, and *timeROC*. A two-tailed P-value of <0.05 was considered statistically significant.

Results

Prevalence of atrial fibrillation in heart failure with preserved ejection fraction patients

Among 3445 patients with HFpEF in the TOPCAT trial, a total of 1243 subjects had a diagnosis of AF at baseline including a history of AF or AF confirmed on an ECG at enrolment. Of these subjects, the mean age was 71.3 ± 9.2 years, and 45.6% were women (*Table 1*). The mean CHADS2, R2CHADS2, and CHA2DS2-VASc scores were 2.8, 3.7, and 4.3 points, respectively. The AF prevalence rate in HFpEF patients across the CHADS2, R2CHADS2, and CHA2DS2-VASc score categories is shown in Supporting Information, *Figure S1*. Overall, the prevalence rate of AF was 36.1% in HFpEF patients.

Incidence of new-onset atrial fibrillation in heart failure with preserved ejection fraction patients

A total of 2202 HFpEF patients without pre-existing AF at baseline (mean age: 67.0 ± 9.4 years; female ratio: 54.9%) were followed to examine the incidence of new-onset AF. The baseline patient characteristics are shown in *Table 1*. The mean CHADS2, R2CHADS2, and CHA2DS2-VASc scores of 2202 HFpEF patients were 2.6, 3.3, and 4.1 points, respectively. During a median follow-up of 3.3 (interquartile range, 2.0–4.9) years, 5.9% of patients (130/2202) had an event of incident AF. The distributions of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores in HFpEF patients are shown in

Supporting Information, *Figure S2*. The incidence of AF across the three studied scores is presented in Supporting Information, *Table S1*. Overall, the average incidence of AF was 1.80 (95% CI: 1.5–2.1) per 100 patient-years in HFpEF patients.

Characteristics of heart failure with preserved ejection fraction patients with or without incident atrial fibrillation

As shown in *Table 2*, compared with patients without incident AF, those with incident AF were older, had a greater proportion of age ≥75 years, had lower heart rate, diastolic blood pressure, body mass index, waist circumference and estimated glomerular filtration rate, and had more co-morbidities including vascular diseases, dyslipidaemia, diabetes mellitus, and renal dysfunction. Baseline echocardiographic data were available in 565 patients. Compared with patients without incident AF, those with incident AF had larger left atrial volume index (31.2 ± 10.0 vs. 26.1 ± 9.3 mL/m^2, P = 0.002; Supporting Information, *Table S2*). There were no differences in the remaining echocardiographic parameters between the two studied groups. Because the patients with incident AF were too low in sample size (38 patients) to have meaningful comparisons with patients without incident AF, the corresponding data should be interpreted cautiously and confirmed in subsequent studies.

Associations of CHADS2, R2CHADS2, and CHA2DS2-VASc with incident atrial fibrillation

The associations of individual components in the CHADS2, R2CHADS2, and CHA2DS2-VASc scores with new-onset AF are shown in Supporting Information *Table S3*. In the multivariable competing risk models, the age of ≥75 years and diabetes mellitus were independently associated with the risk of incident AF. When score was analysed as a continuous variable, per 1-point increase in the CHADS2 (HR 1.42, 95% CI: 1.20–1.68), R2CHADS2 (HR 1.25, 95% CI: 1.10–1.42), or CHA2DS2-VASc (HR 1.30, 95% CI: 1.16–1.46) scores was associated with an increased risk of incident AF (*Table 3*). When score was analysed as a categorical variable, the cumulative incidence of AF was increased in patients with CHADS2 ≥ 3, R2CHADS2 ≥ 3, or CHA2DS2-VASc ≥ 4 (*Figure 1*). Compared with the corresponding controls, patients with CHADS2 ≥ 3 (HR 2.62, 95% CI: 1.70–4.04), R2CHADS2 ≥ 3 (HR 2.55, 95% CI: 1.56–4.17), or CHA2DS2-VASc ≥ 4 (HR 2.54, 95% CI: 1.59–4.07) was associated with a higher risk of incident AF (*Table 3*).

Table 1 Clinical characteristics of HFpEF patients with or without pre-existing diagnosis of AF at baseline

	With baseline AF (n = 1243)	Without baseline AF (n = 2202)
Age		
Age, years	71.3 ± 9.2	67.0 ± 9.4
Age ≥75 years, n	487 (39.2)	514 (23.3)
Females, n	570 (45.9)	1205 (54.7)
White race, n	1139 (91.6)	1923 (87.3)
Heart rate, b.p.m.	70 (62, 78)	68 (61, 75)
SBP, mmHg	130 (120, 136)	130 (120, 140)
DBP, mmHg	76 (68, 80)	80 (70, 84)
BMI, kg/m^2	31.2 (27.3, 36.0)	30.8 (27.1, 35.6)
Waist circumference, cm	104 (96, 117)	103 (93, 114)
Smoking ever, n	616 (49.6)	1012 (46.0)
NYHA functional class, n		
III and IV	487 (39.2)	651 (29.6)
eGFR, mL/(min*1.73 m^2)	63.0 (51.5, 76.5)	66.9 (55.3, 80.7)
Co-morbidities, n (%)		
Previous HF hospitalization	857 (68.9)	1634 (74.2)
Previous stroke	119 (9.6)	146 (6.6)
Previous MI	261 (21.0)	634 (28.8)
PAD	103 (8.3)	217 (9.9)
Vascular diseases[a]	326 (26.2)	753 (34.2)
Dyslipidaemia	779 (62.7)	1297 (58.9)
Hypertension	1126 (90.6)	2024 (91.9)
COPD	172 (13.8)	231 (10.5)
Asthma	78 (6.3)	145 (6.6)
Diabetes mellitus	369 (29.7)	752 (34.2)
Thyroid diseases	268 (21.6)	274 (12.4)
Renal dysfunction[b]	551 (44.3)	781 (35.5)
Risk scores		
CHADS$_2$	2.8 ± 1.0	2.6 ± 0.9
R2CHADS2	3.7 ± 1.5	3.3 ± 1.4
CHA2DS2-VASc	4.3 ± 1.4	4.1 ± 1.3
Medications, n (%)		
ACE-I or ARB	1022 (82.2)	1881 (85.4)
Beta-blocker	948 (76.3)	1729 (78.5)
Calcium channel blocker	420 (33.8)	875 (39.7)
Diuretic	1091 (87.8)	1729 (78.5)
Long acting nitrate	163 (13.1)	352 (16.0)
Statin	663 (53.3)	1143 (51.9)
Aspirin	630 (50.7)	1623 (73.7)
Warfarin	699 (56.2)	88 (4.0)
Dabigatran	19 (1.5)	2 (0.1)
Heparin	13 (1.0)	13 (0.6)

Values are n (%), mean ± SD, or median (interquartile range).
ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; SBP, systolic blood pressure.
[a]Defined as history of myocardial infarction or peripheral arterial disease.
[b]Defined as estimated glomerular filtration rate <60 mL/(min*1.73 m^2).

Performances of CHADS2, R2CHADS2, and CHA2DS2-VASc in predicting incident atrial fibrillation

As shown in *Figure 2*, the C-indexes for the CHADS2, R2CHADS2, and CHA2DS2-VASc scores in predicting incident AF were 0.71 (95% CI: 0.66–0.76), 0.69 (95% CI: 0.64–0.74), and 0.70 (95% CI: 0.65–0.75), respectively. In addition, we compared C-indexes of the two different risk scores using the Z-statistic. The corresponding comparisons were CHADS2 versus R2CHADS2 (Z-statistic: 0.55, P > 0.05), R2CHADS2 versus CHA2DS2-VASc (Z-statistic: 0.28, P > 0.05), and CHADS2 versus CHA2DS2-VASc (Z-statistic: 0.28, P > 0.05), demonstrating no statistically significant differences in the C-indexes among the three studied risk scores.

Discussion

In this study, our data based on a retrospective analysis of the TOPCAT trial indicated that (i) HFpEF patients were at an increased risk of incident AF with an average incidence rate of 1.80 per 100 patient-years; (ii) per 1-point increase

Table 2 Clinical characteristics of HFpEF patients with and without incident AF during follow-up

	Without incident AF (n = 2072)	With incident AF (n = 130)	P value
Age			
Age, years	66.7 ± 9.4	72.4 ± 8.8	<0.001
Age ≥75 years, n	452 (21.8)	62 (47.7)	<0.001
Female, n	1145 (55.3)	60 (46.2)	0.053
White race, n	1813 (87.5)	110 (84.6)	0.41
Heart rate, b.p.m.	68 (62, 75)	64 (60, 74)	0.004
SBP, mmHg	130 (120, 140)	130 (120, 140)	0.98
DBP, mmHg	80 (70, 84)	73 (62, 80)	<0.001
BMI, kg/m^2	30.5 (27.1, 35.3)	33.1 (28.0, 37.8)	0.006
Waist circumference, cm	102.0 (92, 114)	108(98, 122)	<0.001
Ever smoking, n	941 (45.4)	71 (54.6)	0.051
NYHA functional class, n			
III and IV	607 (29.3)	44 (33.8)	0.32
eGFR, mL/(min*1.73 m^2)	67.1 (55.6, 81.0)	62.8 (50.9, 76.9)	0.014
Co-morbidities, n (%)			
Previous HF hospitalization	1554 (75.0)	80 (61.5)	0.001
Previous stroke	135 (6.5)	11 (8.5)	0.49
Previous MI	593 (28.6)	41 (31.5)	0.54
PAD	193 (9.3)	24 (18.5)	0.001
Vascular diseases[a]	696 (33.6)	57 (43.8)	0.022
Dyslipidaemia	1206 (58.2)	91 (70.0)	0.010
Hypertension	1905 (91.9)	119 (91.5)	1.00
COPD	212 (10.2)	19 (14.6)	0.151
Asthma	136 (6.6)	9 (6.9)	1.00
Diabetes mellitus	690 (33.3)	62 (47.7)	0.001
Thyroid diseases	254 (12.3)	20 (15.4)	0.36
Renal dysfunction[b]	720 (34.7)	61 (46.9)	0.007
Medications, n (%)			
ACE-I or ARB	1777 (85.8)	104 (80.0)	0.09
Beta-blocker	1621 (78.2)	108 (83.1)	0.23
Calcium channel blocker	818 (39.5)	57 (43.8)	0.37
Diuretic	1617 (78.0)	112 (86.2)	0.038
Long acting nitrate	329 (15.9)	23 (17.7)	0.67
Statin	1058 (51.1)	85 (65.4)	0.002
Aspirin	1521 (73.4)	102 (78.5)	0.24
Warfarin	80 (3.9)	8 (6.2)	0.29

Values are n (%), mean ± SD, or median (interquartile range).
ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; SBP, systolic blood pressure.
[a]Defined as history of myocardial infarction or peripheral arterial disease.
[b]Defined as estimated glomerular filtration rate <60 mL/(min*1.73 m^2).

in the CHADS2, R2CHADS2, or CHA2DS2-VASc scores was associated with an increased risk of new-onset AF; (iii) patients with higher CHADS2, R2CHADS2, or CHA2DS2-VASc scores had higher incidence rates of AF; and (iv) the CHADS2, R2CHADS2, and CHA2DS2-VASc scores had modest abilities for predicting incident AF. Overall, our data first suggest that the CHADS2, R2CHADS2, and CHA2DS2-VASc scores could predict the risk of incident AF in HFpEF patients with modest predictive abilities.

Comparisons with previous studies

Patients with HFpEF often have a series of morbidities such as AF. A couple of studies have demonstrated that the prevalence of AF increased with increasing EF from HFrEF to HFpEF. In our current study, 36.1% of HFpEF patients had an AF at admission, which is similar to the AF prevalence reported in the European Society of Cardiology-Heart Failure (ESC-HF) long-term registry (39%)[4] and the Candesartan in Heart failure-Assessment of moRtality and Morbidity (CHARM) trial (31.3%).[6] Additional studies reported a relatively higher prevalence rate of AF such as 45.2% in the Korean Acute Heart Failure registry[3] and 65% in the SwedeHF registry.[21] The prevalence of AF in patients with HFpEF might vary among the populations from different regions or ages.[3] Previously, Kuczaj et al.[22] found that the CHA2DS2-VASc score could be used to detect patients with decompensated HF characterized by the highest prevalence of AF. In our study, the AF prevalence rates in HFpEF patients with a score of ≥3 increased in a graded manner across the CHADS2 (range: 39.1–56.7%), R2CHADS2 (range: 35.9– 71.4%), or CHA2DS2-VASc (range: 28.0–50.0%) score categories.

Table 3 Associations of the CHADS2, R2CHADS2 and CHA2DS2-VASc with incident atrial fibrillation in HFpEF patients

| | Events, n (%) | Person-years | Incidence rates, per 100 person-years | Hazard ratios (95% CIs) | | | | C-indexes |
				Crude	P	Adjusted[a]	P	
CHADS2								
Overall[b]	130 (5.9)	7264	1.8 (1.5–2.1)	1.60 (1.38–1.85)	<0.001	1.42 (1.20–1.68)	<0.001	0.71 (0.66–0.76)
<3	33 (3.0)	3959	0.8 (0.6–1.2)	Ref.	—	Ref.	—	—
≥3	97 (9.0)	3305	2.9 (2.4–3.6)	3.30 (2.21–4.90)	<0.001	2.62 (1.70–4.04)	<0.001	—
R2CHADS2								—
Overall[b]	130 (5.9)	7264	1.8 (1.5–2.1)	1.35 (1.21–1.51)	<0.001	1.25 (1.10–1.42)	<0.001	0.69 (0.64–0.74)
<3	22 (2.6)	2928	0.8 (0.5–1.1)	Ref.	—	Ref.	—	—
≥3	108 (7.9)	4336	2.5 (2.0–3.0)	3.16 (1.99–5.00)	<0.001	2.55 (1.56–4.17)	<0.001	—
CHA2DS2-VASc								—
Overall[b]	130 (5.9)	7264	1.8 (1.5–2.1)	1.39 (1.25–1.54)	<0.001	1.30 (1.16–1.46)	<0.001	0.70 (0.65–0.75)
<4	22 (2.8)	2774	0.8 (0.5–1.2)	Ref.	—	Ref.	—	—
≥4	108 (7.7)	4490	2.4 (2.0–2.9)	2.92 (1.84–4.62)	<0.001	2.54 (1.59–4.07)	<0.001	—

CI, confidence interval; HFpEF, heart failure patients with preserved ejection fraction.
[a]Adjusted for gender (not applicable for CHA2DS2-VASc score), smoking ever, waist circumference, heart rate, diastolic blood pressure, vascular diseases (not applicable for CHA2DS2-VASc score), renal dysfunction (defined as estimated glomerular filtration rate <60 mL/[min*1.73 m^2]; not applicable for R2CHADS2 score).
[b]Scores were used as continuous variable while deriving hazard ratios.

Figure 1 Cumulative incidence curves of incident atrial fibrillation in patients with HFpEF according to (A) CHADS2, (B) R2CHADS2, and (C) CHA2DS2-VASc scores. CIF, cumulative incidence function; HFpEF = heart failure patients with preserved ejection fraction.
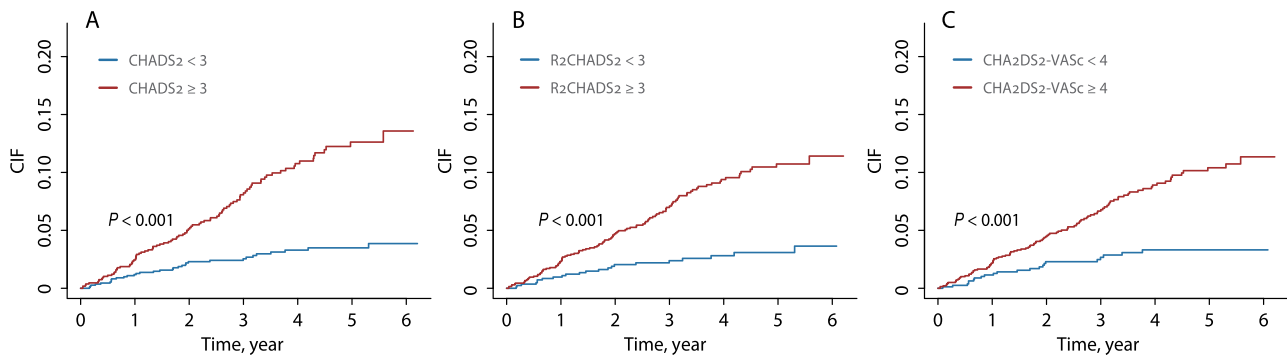
In the general population, prior studies have proposed several risk models that specifically been derived for predicting incident AF such as the Framingham risk score, the Atherosclerosis Risk In Communities Study (ARIC) score, CHADS2, CHA2DS2-VASc, and CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology).[23] A systematic review by Himmelreich *et al.*[23] has summarized all of these 10 risk models (Supporting Information, *Figure S3*), suggesting that the CHARGE-AF score seems to be the most suitable tool for screening AF in the community. In addition, Himmelreich *et al.*[23] also found that the CHADS2 and CHA2DS2-VASc scores have also been used to predict incident AF in the general population, where the pooled C-indexes for the CHADS2 and CHA2DS2-VASc scores were 0.66 (95% CI: 0.59–0.74), and 0.69 (95% CI: 0.64–0.74), respectively.

In recent years, several studies have suggested that the CHADS2 or CHA2DS2-VASc scores could predict AF in patients with AF ablation[16] or those with ST elevation myocardial infarction.[18] However, a clinical risk score for predicting incident AF in HFpEF remains to be established. Our previous study based on the data of the TOPCAT trial indicated that the CHA2DS2-VASc scores were independent predictors of adverse events including stroke, hospitalization, and death in patients with HFpEF.[24] In our current study, both the CHADS2 and CHA2DS2-VASc scores were independent predictors of incident AF. The predictive ability of CHADS2 in HFpEF patients seems to be better than that in the general population (C-index: 0.71 vs. 0.66[23]), while the performance of CHA2DS2-VASc in these two populations is similar (C-index: 0.70 vs. 0.69[23]). The R2CHADS2 score, a proposed stroke risk scoring system by including renal function, seemingly has a better diagnostic capacity than the CHADS2 and CHA2DS2-VASc scores among AF patients.[11] And subsequently, Kornej *et al.*[16] found that the R2CHADS2 score was associated with rhythm outcomes after catheter ablation of AF. There is a dearth of study to determine the performance

Figure 2 Receiver operating characteristic curve for predicting incident atrial fibrillation in patients with HFpEF based on CHADS2, R2CHADS2, and CHA2DS2-VASc scores. AUC, area under the receiver operating characteristic curve; HFpEF, heart failure patients with preserved ejection fraction.
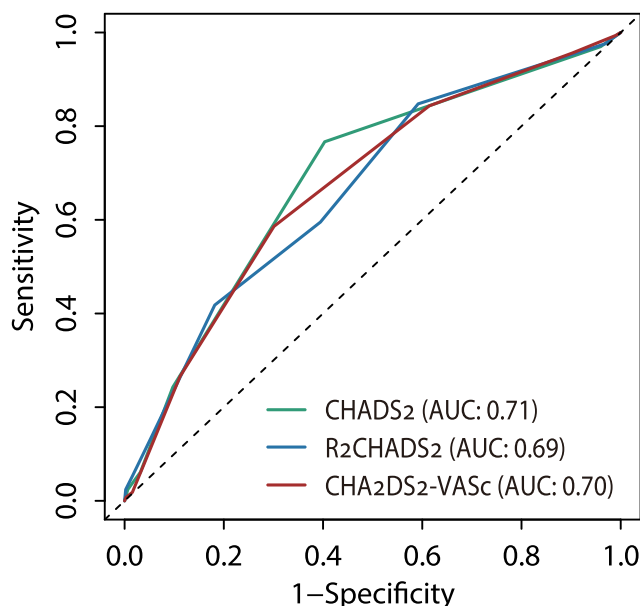
of R2CHADS2 for predicting AF in patients with HFpEF. Herein, we found that the R2CHADS2 score could modestly predict incident AF in HFpEF patients. Lastly, results from *Z*-statistics suggested no differences in the predictive abilities of incident AF among the CHADS2, R2CHADS2, and CHA2DS2-VASc scores.

Implications and further research

HFpEF patients with AF have higher risks of mortality and morbidity than those without AF. The high risk of AF-related stroke in HFpEF patients justifies the need for a well-scheduled screening tool so that oral anticoagulation therapy can be initiated without delay. Although there is still no clinical risk score for AF prediction in HFpEF patients, our current data suggested that the CHADS2, R2CHADS2, and CHA2DS2-VASc scores seemingly could be used for AF detection in this population. Early identification of AF in HFpEF patients through a risk stratification tool may help optimize therapeutic approaches for a better prognosis. Because the predictive abilities of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores are still modest, future studies are needed to confirm the clinical utility of these scores in patients with HFpEF. Also, we could explore the modified scores to obtain a better performance for AF prediction in HFpEF patients. Development of aged rats of HFpEF has suggested that aging-related atrial remodelling and HFpEF are related with nodal dysfunction, atrial enlargement and fibrosis, and conduction abnormalities, which are the potential substrates

for AF.[25,26] The causal pathways of developing AF in HFpEF are still poorly defined and deserve further researches.

Strengths and limitations

This was the first study designed to assess the associations of the CHADS2, R2CHADS2, and CHA2DS2-VASc scores with incident AF in symptomatic HFpEF patients using the competing risk models. Nevertheless, several limitations should be acknowledged in this study. First, due to the nature of a retrospective analysis, the residual confounders from unmeasured factors might influence the validity of our findings. Second, the information about subtypes of AF (i.e., paroxysmal, persistent, or permanent AF) were unavailable herein. There might be some patients with AF episodes in the past but without overt AF at the baseline were included, who are at higher risk for rapid progression to permanent AF,[27] raising the incidence of new-onset AF herein. On the other hand, the events of incident AF were only adjudicated by 12-lead ECG in this trial, which might lead to an underestimate of incidence AF in the follow-up period. Further study involved the use of devices that continuously record heart rhythm (e.g. Holter monitor and implantable loop recorder) could make the analysis more meaningful. Third, most of our included patients were with hypertension, which ultimately increases the risk of AF. The findings should be cautiously extrapolated in normotensive patients. Finally, the number of patients with a high risk score was relatively small due to the limiting sample size, resulting in the lack of a distinct

trend of the incidence rates of incident AF across the score categories. Nevertheless, we have validated the associations of these scores with the risk of incident AF in regression models.

Conclusions

Based on evidence from the TOPCAT trial, the CHADS2, R2CHADS2, and CHA2DS2-VASc scores could predict the risk of incident AF in patients with HFpEF. These scores had modest predictive abilities for incident AF in patients with HFpEF.

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Conflict of interest

All authors declare that they have no conflict of interest.

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Author contributions

Under the direction of Wengen Zhu and Chen Liu, Yuzhong Wu and Zengshuo Xie performed the study design, data extraction, and statistical analysis. Yuzhong Wu wrote the original draft, while Chen Liu revised the draft. All other authors checked the data to ensure accuracy, and edited the manuscript prior to submission to ensure the standard English grammar.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Incidence rates of incident AF in HFpEF patients according to CHADS2, R2CHADS2 and CHA2DS2-VASc scores
Table S2. Baseline characteristics of the patients in echocardiography cohort with and without incident AF during follow-up
Table S3. Multivariate regression models for the associations between individual components risk factors of the CHADS2, R2CHADS2 and CHA2DS2-VASc score and incident AF
Figure S1. The AF prevalence rate in HFpEF patients across the CHADS2, R2CHADS2, and CHA2DS2-VASc score categories
Figure S2. The distributions of the CHADS2, R2CHADS2 and CHA2DS2-VASc scores in HFpEF patients
Figure S3. Characteristics of included risk models developed for incident atrial fibrillation

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