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ORIGINAL RESEARCH ARTICLE

Value of the CHA_2DS_2-VASc score for predicting outcome in patients with heart failure

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Abstract

Aims Comorbidities are highly prevalent in patients with heart failure (HF) and affect clinical outcome. The CHA_2DS_2-VASc score is a validated score to estimate assessment of thromboembolic risk in patients with atrial fibrillation.

Methods and results We evaluated the predictive value of this score on clinical outcome in patients with HF. All patients with a diagnosis of chronic HF at a health maintenance organization were evaluated for the CHA_2DS_2-VASc score. Patients were followed for cardiac related hospitalizations and death. The cohort included 7106 HF patients. Mean follow-up was 744 days; the median CHA_2DS_2-VASc score was 5.0 (range 4.0–6.0). The CHA_2DS_2-VASc score was a significant predictor of survival and predictive of the combined end point of death and cardiovascular hospitalization. Survival rates were reduced with increasing quintiles of the CHA_2DS_2-VASc score: 93.6 ± 0.7% vs. 83.0 ± 1.1% vs. 75.7 ± 1.0% vs. 73.0 ± 1.2% vs. 63.3 ± 1.2%, respectively $P < 0.001$. After adjustment for other significant predictors, increasing CHA_2DS_2-VASc scores were independently predictive of survival and of the combined end point of death and cardiovascular hospitalization by Cox regression analysis. Analysing the CHA_2DS_2-VASc score as a continuous parameter by cox regression analysis demonstrated a significant increase with each point increase in the CHA_2DS_2-VASc score (hazard ratio 1.21, 95% confidence interval 1.17–1.26, $P < 0.0001$). Cox regression analysis using restricted cubic splines demonstrated an independent continuous increase in mortality with increasing CHA_2DS_2-VASc score ($P < 0.0001$ adjusted linear model). The predictive value was present in HF with reduced as well as preserved ejection fraction.

Conclusions The CHA_2DS_2-VASc score has a significant impact on outcome in HF patients.

Keywords CHA_2DS_2-VASc score; Heart failure; Outcome

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Introduction

Heart failure (HF) has emerged as a major epidemic and is a significant public health burden. It is associated with considerable morbidity and mortality.[1] Prognostic factors in this population include parameters specific for HF such as New York Heart Association (NYHA) class and left ventricle ejection fraction but also multiple comorbid conditions that complicate management and adversely affect clinical outcome.[2] The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity programme identified 21 different independent predictors of mortality or morbidity in HF. The most powerful predictors for mortality in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity programme were older age, diabetes, and ejection fraction, and the first two were comorbid conditions.[3]

The CHA_2DS_2-VASc score [congestive HF; hypertension; age $\geq$ 75 years (doubled); type 2 diabetes; previous stroke or transient ischemic attack (doubled); vascular disease; age 65–74 years; and sex category] has been used for the assessment of thromboembolic risk and to guide antithrombotic treatment in patients with atrial fibrillation (AF).[4] This simple and well-established score has been shown to predict risk for other conditions beyond its original field. Several studies have demonstrated an association between the CHA_2DS_2-VASc score and adverse outcomes in several cardiovascular conditions such as chest pain,[5] acute coronary syndrome,[6,7] acute

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myocardial infarction,[8] and pulmonary emboli,[9] regardless of the presence of AF.

The CHA_2DS_2-VASc is a simple score to calculate and could be expected to have an impact on outcome in HF. There are a limited number of studies that evaluated the prognostic significance of the CHA_2DS_2-VASc in patients with HF[10–15] with emphasis on stroke and mortality. The majority assessed mortality in hospitalized patients,[12–15] and only one study evaluated its impact on hospitalizations.[10] Analysis of patients enrolled in the warfarin vs. aspirin in reduced cardiac ejection fraction (WARCEF) trial found that The CHA_2DS_2-VASc score predicted adverse outcomes in patients with systolic HF in sinus rhythm.[13] In addition, Paoletti Perini *et al*. showed that in patients who are candidates for cardiac resynchronization therapy, CHA_2DS_2-VASc score is an independent predictor of major clinical events including death and HF hospitalizations at long term follow-up.[10] There is limited data regarding CHA_2DS_2-VASc score in ambulatory stable patients with chronic HF and the predictive value on HF outcomes including mortality and cardiovascular hospitalizations.

The purpose of the present study was to evaluate the CHA_2DS_2-VASc score as a predictor for cardiovascular outcomes in a large real-world cohort of patients with chronic HF.

Methods

Clalit Health Services is the largest health maintenance organization (HMO) in Israel. It has a central computerized database in which all members have a complete digital record. The database includes demographic data, comprehensive clinical data, all diagnoses, and all laboratory data undertaken in a single centralized laboratory of the HMO. We identified and retrieved electronically from the computerized database all members with a diagnosis of HF as coded by the database in Jerusalem using the International Classification of Diseases, Ninth Revision (ICD-9) code 428. Data were retrieved from January 2017. Patients were followed for clinical events including cardiovascular hospitalizations and death until to January 2019. Seven thousand one hundred six patients had a diagnosis of HF. Natriuretic peptides are not routinely performed in Israel and were not available for analysis. The type of HF (HF with reduced ejection fraction and HF with preserved ejection fraction (HFpEF) was based on a documented specific diagnosis and was available in 67% of the patients. The diagnosis of the remaining patients was 'HF, unspecified'. All hospitalizations in cardiac and internal medicine departments including cardiac and internal intensive care units were retrieved and analysed. Data on mortality were retrieved from the National Census Bureau. The Institutional Committee for Human Studies of Clalit Health Services, approved the study protocol.

Biochemical analyses were performed at the HMO single centralized core laboratory with routine standardized methodologies on fresh samples of blood obtained after an overnight fast. Glucose levels were measured in plasma, and all other biochemical analyses were performed on serum. Urinary albumin to creatinine ratio (μg/mg) was measured from a spot morning urine sample. The laboratory is authorized to perform tests according to the international quality standard ISO-9001.

SPSS Version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and R Statistical Software Version 3.0.1 for Windows (R Development Core Team) were used for the analyses. Comparison of the clinical characteristics was performed using the Mann–Whitney *U* test for continuous variables and the Chi-square test for categorical variables. Clinical predictors were transformed where appropriate. Log_{10} was used for logarithmic transformations with the exception of estimated glomerular filtration rate that a square root transformation was used. Follow-up time was calculated using Kaplan–Meier estimate of potential follow-up. Kaplan–Meier curves, with the log-rank test, were used to compare survival according to CHA_2DS_2-VASc score. Multivariate Cox proportional hazards regression analysis was used to evaluate independent variables that determined survival. Parameters included in the multivariate Cox regression analysis incorporated relevant parameters that were significant on univariable analysis with the addition of significant drug therapy in separate models. Restricted cubic spline multivariable cox regression analysis was performed to evaluate the relationship between CHA_2DS_2-VASc score as a continuous parameter and mortality. Proportionality assumptions of the Cox regression models were evaluated by log–log survival curves and with the use of Schoenfeld residuals. An evaluation of the existence of confounding or interactive effects was made between variables and their possible collinearity. A P value of <0.05 was considered statistically significant.

Results

Clinical parameters

The study cohort included 7106 HF patients. Supporting Information *Figure* S1 demonstrates the distribution of the CHA_2DS_2-VASc score in the HF cohort. The mean CHA_2DS_2-VASc score was 5.1 ± 1.8, median 5.0 (interquartile range 4.0–6.0). We divided the cohort into five quintiles based on the CHA_2DS_2-VASc score: $\leq$3, 4, 5, 6, and $\geq$7. The characteristics of the patients stratified according to the CHA_2DS_2-VASc score quintiles are presented in *Table* 1. Patients with a higher CHA_2DS_2-VASc score were more likely to be women, older, and with a higher number of comorbidities including AF. A higher CHA_2DS_2-VASc score was associated with more

Table 1 Demographics and clinical characteristics of patients with heart failure according to the CHA_2DS_2-VASc score

Variable	CHA_2DS_2-VASc ≤3 (*N* = 1231)	CHA_2DS_2-VASc 4 (*N* = 1182)	CHA_2DS_2-VASc 5 (*N* = 1712)	CHA_2DS_2-VASc 6 (*N* = 1456)	CHA_2DS_2-VASc ≥7 (*N* = 1525)	Total (*N* = 7106)	*P* Value
Age (years)	59 (50–65)	70 (62–77)	79 (71–86)	82 (77–87)	83 (78–88)	77 (67–85)	<0.001
Gender (male)	957 (78)	798 (68)	872 (51)	584 (40)	521 (34)	3732 (53)	<0.001
NYHA Class III/IV	181 (21)	274 (30)	521 (41)	489 (45)	543 (48)	2008 (38)	<0.001
HF with reduced ejection fraction	411 (54)	358 (47)	462 (38)	335 (36)	347 (34)	1913 (41)	<0.001
Diabetes mellitus	284 (23)	563 (48)	824 (48)	1033 (71)	1091 (72)	3795 (53)	<0.001
Hypertension	445 (36)	937 (79)	1608 (94)	1407 (97)	1507 (99)	5904 (83)	<0.001
Hyperlipidaemia	892 (72)	1040 (88)	1533 (90)	1383 (95)	1467 (96)	6315 (89)	<0.001
Ischemic heart disease	615 (50)	742 (63)	1062 (62)	1048 (72)	1198 (79)	4665 (66)	<0.001
Prior myocardial infarction	330 (27)	412 (35)	632 (37)	725 (50)	915 (60)	3014 (42)	<0.001
Prior coronary bypass surgery	31 (3)	28 (2)	28 (2)	16 (1)	19 (1)	122 (2)	0.01
Atrial fibrillation	246 (20)	388 (33)	692 (40)	643 (44)	740 (49)	2709 (38)	<0.001
Prior stroke/transient ischemic attack	7 (0.6)	47 (4)	111 (6)	289 (20)	1225 (80)	1679 (24)	<0.001
Peripheral vascular disease	28 (2)	96 (8)	206 (12)	280 (19)	446 (29)	1056 (15)	<0.001
Chronic obstructive lung disease	204 (17)	275 (23)	405 (24)	342 (23)	325 (21)	1551 (22)	<0.001
Charlson score	3.0 (2.0–4.0)	5.0 (4.0–6.0)	6.0 (5.0–7.0)	7.0 (6.0–8.0)	8.0 (7.0–9.0)	6.0 (5.0–8.0)	<0.001
Depression	108 (9)	139 (12)	315 (18)	309 (21)	429 (28)	1300 (18)	<0.001
Dementia	28 (2)	82 (7)	236 (14)	256 (18)	398 (26)	1000 (14)	<0.001
Dialysis	43 (3)	82 (7)	95 (6)	77 (5)	97 (6)	394 (6)	0.003
Malignancy	143 (12)	233 (20)	422 (25)	362 (25)	404 (26)	1564 (22)	<0.001
Body mass index (kg/m^2)	28 (24–32)	29 (26–33)	29 (26–34)	29 (26–33)	29 (25–32)	29 (25–33)	<0.001
Pulse (beats per minute)	76 (67–85)	73 (64–80)	72 (64–80)	70 (64–79)	71 (64–79)	72 (64–80)	<0.001
Systolic blood pressure (mmHg)	122 (112–131)	126 (117–135)	129 (119–140)	130 (120–140)	130 (120–140)	128 (118–139)	<0.001
Diastolic blood pressure (mmHg)	73 (66–80)	72 (65–80)	70 (64–79)	70 (63–79)	70 (63–79)	71 (65–79)	<0.001
Laboratory Data							
Creatinine (mg/dL)	0.9 (0.7–1.0)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.0 (0.8–1.3)	<0.001
Estimated glomerular filtration rate (mL/min per $1.73m^2$)[a]	94 (76–112)	76 (55–95)	67 (49–87)	61 (42–80)	58 (40–78)	69 (48–92)	<0.001
Urea (mg/dL)	0.9 (0.7–1.0)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.1 (0.8–1.5)	1.0 (0.8–1.3)	<0.001
Urine Albumin/Creatinine ratio	15 (7.0–63)	34 (11–171)	38 (13–160)	46 (17–173)	60 (20–241)	38 (13–161)	<0.001
Sodium (mEq/L)	140 (139–142)	140 (138–142)	140 (138–142)	140 (138–142)	140 (138–142)	140 (138–142)	0.006
Potassium (mEql/L)	4.5 (4.3–4.8)	4.6 (4.3–4.9)	4.6 (4.3–5.0)	4.6 (4.3–5.0)	4.6 (4.3–5.0)	4.6 (4.3–4.9)	<0.001
Haemoglobin (g/dL)	14 (13–15)	13 (12–14)	13 (11–14)	12 (11–13)	12 (11–13)	13 (11–14)	<0.001
White blood count ($x10^9/L$)	7.6 (6.2–9.2)	7.4 (6.1–8.9)	7.1 (5.9–8.6)	7.3 (6.1–8.7)	7.2 (5.9–8.9)	7.3 (6.0–8.8)	<0.001
Red cell distribution width (%)	14 (14–15)	15 (14–16)	15 (14–16)	15 (14–16)	15 (14–17)	15 (14–16)	<0.001
Glucose (mg/dL)	99 (91–113)	107 (95–137)	105 (94–131)	112 (95–141)	110 (95–143)	106 (94–133)	<0.001
Haemoglobin A1c (%)	5.7 (5.3–6.2)	6.1 (5.6–7.3)	6.0 (5.6–7.0)	6.3 (5.7–7.4)	6.4 (5.7–7.4)	6.1 (5.6–7.1)	<0.001
Uric acid (mg/dL)	5.9 (4.9–7.0)	6.2 (5.2–7.5)	6.3 (5.1–7.6)	6.5 (5.3–7.9)	6.5 (5.2–7.9)	6.3 (5.1–7.6)	<0.001
TSH (mIU/L)	2.0 (1.4–3.1)	2.2 (1.4–3.3)	2.3 (1.5–3.5)	2.3 (1.4–3.5)	2.4 (1.5–3.5)	2.2 (1.5–3.4)	<0.001
Iron (μg/dL)	68 (48–90)	61 (44–81)	58 (42–78)	55 (41–71)	55 (38–70)	58 (42–77)	<0.001
Transferrin (mg/dL)	260 (232–297)	248 (214–294)	246 (211–289)	244 (208–284)	236 (201–275)	245 (210–285)	<0.001
Transferrin saturation (%)	18 (13–26)	17 (12–24)	17 (12–23)	16 (12–22)	16 (11–22)	17 (12–23)	<0.001
Ferritin (ng/ml)	88 (40–189)	92 (40–180)	82 (38–168)	78 (39–176)	86 (39–187)	84 (39–179)	0.23
Calcium (mg/dL)	9.3 (9.1–9.6)	9.3 (8.9–9.6)	9.2 (8.9–9.5)	9.2 (8.9–9.5)	9.2 (8.8–9.5)	9.2 (8.9–9.6)	<0.001
Phosphorus (mg/dL)	3.4 (3.0–3.8)	3.5 (3.1–3.9)	3.5 (3.1–3.9)	3.5 (3.2–3.9)	3.6 (3.2–4.0)	3.5 (3.1–3.9)	<0.001
Magnesium (mg/dL)	2.1 (2.0–2.3)	2.1 (1.9–2.3)	2.1 (2.0–2.3)	2.1 (1.9–2.3)	2.1 (1.9–2.3)	2.1 (1.9–2.3)	0.07
Triglycerides (mg/dL)	120 (87–170)	123 (90–172)	116 (87–160)	120 (89–170)	121 (89–168)	120 (88–168)	0.03
Low-density lipoprotein (mg/dL)	92 (70–116)	84 (66–106)	82 (65–104)	81 (64–103)	79 (62–100)	83 (65–106)	<0.001
Albumin (g/dL)	4.1 (3.9–4.3)	4.0 (3.7–4.2)	3.9 (3.6–4.1)	3.8 (3.5–4.1)	3.7 (3.4–4.0)	3.9 (3.6–4.1)	<0.001
C-Reactive protein (mg/dL)	0.5 (0.2–1.3)	0.6 (0.2–1.6)	0.6 (0.3–1.6)	0.6 (0.2–1.7)	0.7 (0.3–1.9)	0.6 (0.3–1.6)	0.002
Alanine transaminase (IU)	20 (15–27)	17 (13–23)	15 (11–20)	14 (11–20)	14 (10–19)	16 (11–22)	<0.001
Alkaline phosphatase (IU)	85 (69–108)	89 (72–112)	90 (71–112)	89 (71–114)	92 (73–117)	89 (71–113)	<0.001
Total bilirubin (mg/dL)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.7)	0.5 (0.4–0.7)	0.6 (0.4–0.8)	<0.001
Gamma-glutamyltransferase (IU)	26 (18–42)	27 (18–47)	26 (18–42)	25 (17–43)	25 (17–50)	26 (18–44)	0.05
Medication							
ACE-I/ARB/ARNI	838 (68)	912 (77)	1316 (77)	1124 (77)	1139 (75)	5329 (75)	<0.001
Beta blockers	827 (67)	883 (75)	1238 (72)	1098 (75)	1107 (73)	5153 (73)	<0.001
Spironolactone	387 (31)	406 (34)	603 (35)	541 (37)	516 (34)	2453 (35)	0.03
Furosemide	494 (40)	718 (61)	1183 (69)	1084 (74)	1136 (74)	4615 (65)	<0.001
Thiazide	82 (7)	173 (15)	249 (15)	208 (14)	208 (14)	920 (13)	<0.001

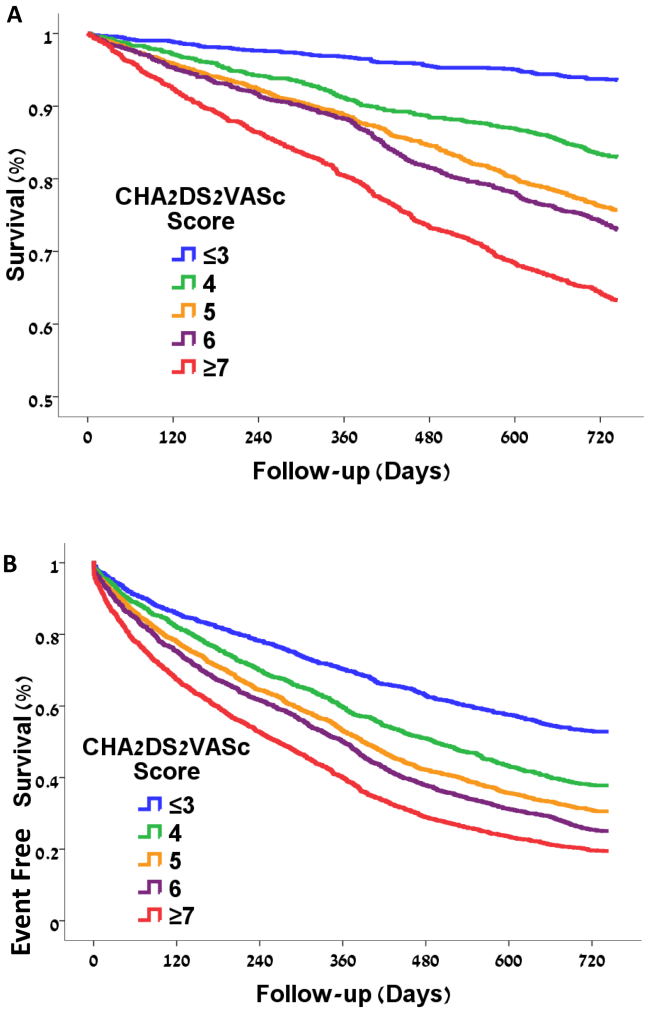
(*Continues*)

Table 1 (continued)

Variable	CHA_2DS_2-VASc ≤3 (*N* = 1231)	CHA_2DS_2-VASc 4 (*N* = 1182)	CHA_2DS_2-VASc 5 (*N* = 1712)	CHA_2DS_2-VASc 6 (*N* = 1456)	CHA_2DS_2-VASc ≥7 (*N* = 1525)	Total (*N* = 7106)	*P* Value
Digoxin	61 (5)	63 (5)	91 (5)	95 (7)	105 (7)	415 (6)	0.11
Amiodarone	142 (12)	176 (15)	291 (17)	245 (17)	237 (16)	1,091 (15)	<0.001
Aspirin	634 (52)	693 (59)	937 (55)	812 (56)	745 (49)	3,821 (54)	<0.001
New oral anticoagulants[b]	131 (11)	253 (21)	484 (28)	454 (31)	506 (33)	1828 (26)	<0.001
Vitamin K antagonists	204 (17)	182 (15)	222 (13)	187 (13)	194 (13)	989 (14)	0.008

HF, heart failure; NYHA, New York Heart Association; TSH, thyroid stimulating hormone.
Data are presented as median (interquartile range) for continuous variables and counts (percentages) for categorical variables. *P* value by the Kruskal–Wallis test for continuous variables and the Chi-square test for categorical variables. Diabetes mellitus defined as fasting plasma glucose ≥126 mg/dL or glucose lowering treatment, hypertension as blood pressure >140/90 mmHg measured on several occasions or anti-hypertensive treatment and hyperlipidemia as low density lipoprotein >130 mg/dL, fasting serum triglycerides >200 mg/dL, or lipid lowering treatment.
[a]Estimated glomerular filtration rate was calculated using the modified modification of diet in renal disease (MDRD) equation ($175 * \text{serum creatinine}^{-1.154} * \text{age}^{-0.203}$. For female patients, a correction factor is used multiplying by 0.742.).
[b]Dabigatran, Rivaroxaban, or Apixaban.

Figure 1 Survival and event-free survival from death and cardiovascular hospitalization by Kaplan–Meier survival analysis stratified by quintiles of CHA_2DS_2-VASc score. (A) Increasing CHA_2DS_2-VASc scores were directly associated with reduced survival; log rank $P < 0.001$. (B) Increasing CHA_2DS_2-VASc scores were directly associated with reduced event-free survival from death or cardiovascular-hospitalizations; log rank $P < 0.001$.



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advanced NYHA class and with HFpEF. Other predictors of a worse outcome in HF were also associated with a higher CHA_2DS_2-VASc score including higher urea and lower estimated glomerular filtration rate, iron, haemoglobin, and albumin. CHA_2DS_2-VASc score had a minor effect on pharmacological therapy with the exception that a higher score was associated with more furosemide therapy.

CHA_2DS_2-VASc score and clinical outcomes

The overall 2 year-mortality rate was 23.2%. Survival rate by Kaplan–Meier analysis suggested that the CHA_2DS_2-VASc score was directly and incrementally associated with reduced survival. Survival rates were reduced with increasing quintiles of the CHA_2DS_2-VASc score: 93.6 ± 0.7% vs. 83.0 ± 1.1% vs. 75.7 ± 1.0% vs. 73.0 ± 1.2% vs. 63.3 ± 1.2%, respectively $P < 0.001$; *Figure* 1A). Similarly, the CHA_2DS_2-VASc score was also directly associated with decreased event-free survival from death or cardiovascular-hospitalizations (52.8 ± 1.4% vs. 37.8 ± 1.4% vs. 30.6 ± 1.1% vs. 25.1 ± 1.1% vs. 19.5 ± 1.0%, $P < 0.001$; *Figure* 1B). Multivariable Cox regression analysis after adjustment for significant predictors demonstrated that CHA_2DS_2-VASc score was a significant predictor of mortality (*Table* 2). After adjustment for other significant predictors (*Table* 2 for predictors included), CHA_2DS_2-VASc score was associated with an incremental increase in mortality. Inclusion of HF medications demonstrated a similar result (Supporting Information, *Table* S1). The CHA_2DS_2-VASc score was also a significant independent predictor of the combined endpoint of death or cardiovascular-hospitalizations with a graded increased risk with increasing CHA_2DS_2-VASc score (*Table* S1). Analysing the CHA_2DS_2-VASc score as a continuous parameter by Cox regression analysis demonstrated a significant increase in mortality with each point increase in the CHA_2DS_2-VASc score after adjustment for clinical parameters and drug therapy (hazard ratio 1.21, 95% confidence interval 1.17–1.26, $P < 0.0001$).

A sensitivity analysis evaluating CHA_2DS_2-VASc score as a continuous parameter using restricted cubic splines was performed. Knots were allocated at CHA_2DS_2-VASc score of 2, 5, 6, and 8. Cox regression analysis demonstrated a direct relationship between the CHA_2DS_2-VASc score and mortality. This analysis demonstrated that there was a continuous increase in the risk with increasing CHA_2DS_2-VASc score (*Figure* 2A), $P < 0.0001$ for the linear model. After adjustment for significant parameters included in *Table* 2, there was a direct linear relationship between CHA_2DS_2-VASc score and mortality, and this was independently significant (*Figure* 2B), $P < 0.0001$ for the adjusted linear model.

The predictive value of the CHA_2DS_2-VASc score was present over the entire cohort of HF patients including patients with HF with reduced ejection fraction and in HFpEF (Supporting Information, *Table* S1). In all groups, the CHA_2DS_2-VASc score was a significant predictor of mortality and was associated with an incremental increase in mortality by itself and after adjustment for significant predictors. A similar result was demonstrated regarding event-free survival from death or cardiovascular hospitalization. Adjustment for other significant predictors demonstrated that the increase in CHA_2DS_2-VASc score was a significant predictor in both

Table 2 Predictors of mortality by Cox regression analysis

	Univariable		Multivariable	
Predictor	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* Value
Age (years)	1.06 (1.05–1.06)	<0.001	/	/
Gender (male)	0.82 (0.74–0.90)	<0.001	/	/
NYHA III/IV	1.74 (1.56–1.94)	<0.001	1.29 (1.14–1.46)	<0.001
Diabetes mellitus	1.16 (1.05–1.28)	0.003	/	/
Hypertension	2.36 (1.99–2.80)	<0.001	/	/
Ischemic heart disease	1.05 (0.95–1.17)	0.33	/	/
Atrial fibrillation	1.61 (1.46–1.77)	<0.001	1.35 (1.20–1.51)	<0.001
Body mass index[a] (kg/m^2)	0.12 (0.07–0.22)	<0.001	0.08 (0.04–0.15)	<0.001
Urea (mg/dL)[a]	12.19 (9.89–15.02)	<0.001	6.53 (4.41–9.68)	<0.001
eGFR[b] (mL/min per $1.73m^2$)	0.82 (0.80–0.84)	<0.001	0.98 (0.96–1.01)	0.20
Sodium (mEq/L)	0.94 (0.92–0.95)	<0.001	0.95 (0.94–0.97)	<0.001
Haemoglobin (g/dL)	0.76 (0.74–0.78)	<0.001	0.86 (0.84–0.89)	<0.001
CHA_2DS_2VASc		<0.001		<0.001
$CHA_2DS_2VASc \leq 3$	1.0 (Reference)		1.0 (Reference)	
CHA_2DS_2VASc 4	2.81 (2.16–3.64)	<0.001	1.92 (1.42–2.60)	<0.001
CHA_2DS_2VASc 5	4.17 (3.28–5.31)	<0.001	2.65 (2.00–3.51)	<0.001
CHA_2DS_2VASc 6	4.71 (3.70–6.00)	<0.001	2.41 (1.81–3.21)	<0.001
$CHA_2DS_2VASc \geq 7$	6.93 (5.48–8.78)	<0.001	3.52 (2.66–4.67)	<0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.
Data are presented as hazard ratio (95% confidence interval), *P* value.
[a]Log-transformed.
[b]Square root-transformed.

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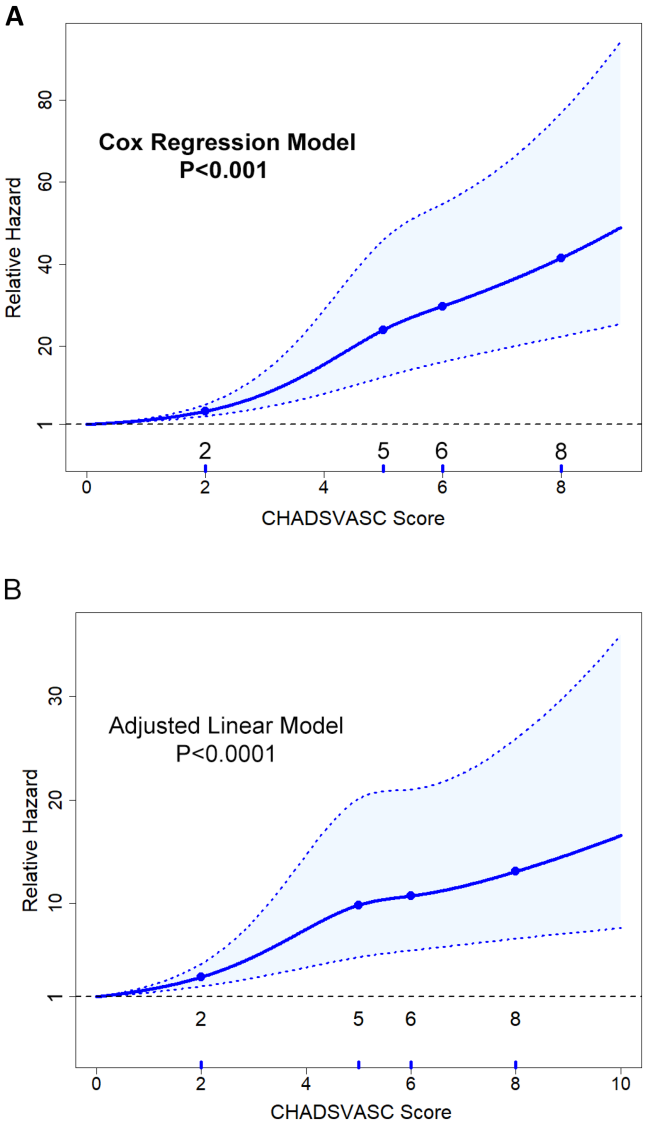
Figure 2 Mortality as a function of CHA_2DS_2-VASc score as a continuous variable using restricted cubic splines. (A) Cox regression analysis with hazard ratio for mortality [with 95% confidence interval]. There was a continuous increase in the risk with increasing CHA_2DS_2-VASc score, $P < 0.0001$ for the linear model. (B) Cox regression analysis for mortality after adjustment, $P < 0.0001$ for the adjusted model. Variables included in the model included New York Heart Association class, atrial fibrillation, log transformed body mass index, log-transformed serum urea levels, square root-transformed estimated glomerular filtration rate, serum sodium, and haemoglobin.



groups. In addition, the CHA2DS2-VASc score was a predictor of outcome in patient regardless of AF. In patients with AF as well as in patients without AF, the CHA_2DS_2-VASc score was predictive of death as well as death and cardiovascular hospitalizations after adjustment for significant predictors (Supporting Information, *Table* S3).

We also looked at the predictive value of the CHA2DS2-VASc score by itself compared with the standard multivariable adjusted model in our cohort using the receiver operator characteristics curve for mortality. Although the adjusted model incorporating numerous HF specific parameters including NYHA class was better than the CHA2DS2-VASc score (area under the curve = 0.765, $P < 0.0001$), the CHA2DS2-VASc had a good predictive value on its own (area under the curve = 0.653, $P < 0.0001$).

Discussion

In this cohort of real-world HF patients, the CHA_2DS_2-VASc score was a significant predictor of death as well as death

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and cardiovascular hospitalizations. There was a direct incremental relationship between CHA_2DS_2-VASc score and clinical outcomes. For example, 2 year survival among patients with CHA_2DS_2-VASc score ≤ 3 was over 93% compared with less than 64% in patients with a score ≥ 7. A similar pattern was observed for the combined end point of mortality and cardiovascular hospitalizations. Moreover, the present study suggests this simple well-known score incorporating readily available clinical parameters conveys predictive value over the whole spectrum of HF patients including patients with preserved as well as reduced ejection fraction and could be useful in estimating outcome in chronic HF patients.

Although the CHA_2DS_2-VASc score is recommended for the assessment of the risk of thromboembolic event in patients with AF, in recent years, it is used to predict outcomes in several other cardiovascular diseases. High CHA_2DS_2-VASc score is associated with worse long term outcomes in patients with coronary disease,[16] acute coronary syndrome,[6] and even in patients who were evaluated for chest pain.[5] It is reasonable to assume that CHA_2DS_2-VASc score is valuable in HF, because its components are prognostic factors in HF.[17]

There are limited data available regarding the CHA_2DS_2-VASc score in predicting HF outcomes in patients with HF. Most of the published studies evaluated embolic events and death in hospitalized HF patients[12–15] demonstrating the value of the CHA_2DS_2-VASc score in predicting mortality. In the Danish prospective cohort study of HF populations with or without AF, the CHA_2DS_2-VASc score was associated with risk of ischemic stroke, thromboembolism, and death.[11] Similar to our findings, data from the Korean Acute Heart Failure (KorAHF) registry, showed in each 1-point increase in CHA_2DS_2-VASc score among hospitalized HF patients, were associated with significantly increased long-term mortality.[15] The present study demonstrates that the CHA_2DS_2-VASc score is not only a predictor of mortality but also predicts the risk of cardiovascular hospitalizations. Similarly, the CHA_2DS_2-VASc score predicted HF hospitalizations in HF patients undergoing cardiac resynchronization therapy.[10]

The burden of comorbidities is significant in patients with HF as seen in the present study. This was particularly evident in patients with HFpEF that was associated with a higher CHA_2DS_2-VASc score. This is to be anticipated, as the typical characteristics of patients with HFpEF are older patients with accompanying comorbidities such as diabetes mellitus and prior stroke.[18] Nevertheless, the predictive value of these comorbidities regarding mortality was not restricted only to patients with HFpEF, suggesting that the CHA_2DS_2-VASc score can be used over the entire spectrum of HF patients.

The present study emphasizes the importance of comorbidities that are part of the CHA_2DS_2-VASc score as central players in driving morbidity and mortality in HF. Comorbidities are highly prevalent in HF and have a major impact on outcome. The reasons for the above phenomena are multifactorial.[18] Several comorbidities such as diabetes mellitus and hypertension predispose or cause HF and, furthermore, are important in the destabilization and progression of HF. Comorbidities and HF have numerous bidirectional interactions and are interrelated by several mechanisms, including inflammation, activation of the sympathetic, and renin-angiotensin-aldosterone system. HF influences comorbidities, with mutual effects, contributing to the progression of HF.

Limitations

Several potential limitations of this study merit consideration. The present study was an observational study. Data regarding clinical parameters and drug therapy were based on a digitized database. Although this database was validated and found to be highly accurate, not all data could be verified. While we tried to adjust for clinically relevant parameters, not all clinical parameters were available, and it is impossible to adjust for all variables that may affect outcome. Data on natriuretic peptide levels were not available. Data on the specific HF type were not available in all of the patients, and this may cause a bias. In addition, the cohort was a community-based cohort, and the findings may not be applicable in more advanced or hospital-based HF cohorts.

Conclusions

In conclusion, given the high variability in clinical and demographic characteristics among patients with HF, the CHA_2DS_2-VASc score calculated at bedside could be incorporated into the routine risk stratification and could be useful in estimating outcome in HF patients.

Conflict of interest

None declared.

Supporting information

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

Figure S1. Histogram of the distribution of the CHA_2DS_2-VASc score in the heart failure cohort.

Table S1. *Hazard ratio for clinical outcome according to CHA_2DS_2-VASc score by Cox regression analysis.*

Table S2. *Hazard ratio for clinical outcome according to CHA_2DS_2-VASc score by Cox regression analysis in subsets of HF types.*

Table S3. *Hazard ratio for clinical outcome according to CHA_2DS_2-VASc score by Cox regression analysis in Patients with and without Atrial Fibrillation.*

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