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Risk stratification using the CHA_2DS_2-VASc score in patients with coronary heart disease undergoing percutaneous coronary intervention; sub-analysis of SHINANO registry ☆

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ABSTRACT

Background: $CHADS_2$ or CHA_2DS_2-VASc score is used for prediction of stroke in patients with atrial fibrillation (AF). Recently, $CHADS_2$ score is reported to have prognostic value in acute coronary syndrome without AF. However, clinical validation of CHA_2DS_2-VASc score for prognostic stratification in coronary heart disease (CHD) without AF remains uncertain. In this study, we evaluate whether CHA_2DS_2-VASc score could predict clinical outcome in CHD without known AF.

Methods: SHINANO registry was a prospective, observational, multicenter cohort study, enrolling 1923 consecutive patients with CHD from August 2012 to July 2013. Two hundred nine patients were excluded because of known AF. We calculated CHA_2DS_2-VASc score in the remaining 1714 patients (mean age 70 ± 11 years, 23% female) without known AF. To assess the clinical validation of CHA_2DS_2-VASc score, we divided patients into 3 groups according to the tertiles (score 0–2, 3–4, and ≥5). The primary endpoint was MACE including death, non-fatal myocardial infarction, and ischemic stroke at 1 year.

Results: One-year follow-up was completed in 1632 patients (95.2%). Cumulative incidence of MACE was 139 cases. In Kaplan–Meier analysis, incidence of MACE was significantly higher in patients with CHA_2DS_2-VASc score ≥5 compared to 3–4 and 0–2 (14.6% vs. 6.8% vs. 5.3%, $p < 0.001$). In multivariate Cox-regression analysis, CHA_2DS_2-VASc score was an independent predictor for MACE (hazard ratio 1.26, 95% confidence interval 1.15–1.39$p < 0.001$).

Conclusions: This study demonstrated that CHA_2DS_2-VASc score could provide prognostic information in CHD without known AF.

1. Introduction

The $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes, ischemic stroke or transient ischemic attack) score is used to stratify the risk of stroke and to determine whether anticoagulants are indicated in patients with atrial fibrillation (AF) [1]. This scoring system is very familiar to physicians because it could be calculated with the data from medical questionnaires. Moreover, the $CHADS_2$ score was reported to have an impact on post-stroke all-cause mortality in patients with or without AF [2]. It has been also reported that the $CHADS_2$ score could have prognostic value with regards to adverse outcome in patients with acute myocardial infarction (MI) [3,4]. Recently, the refined risk stratification for predicting stroke and thromboembolism was assessed in AF and CHA_2DS_2-VASc score has been proposed [5]. The CHA_2DS_2-VASc score has been assessed its clinical validation compared to $CHADS_2$ score and several studies confirmed that CHA_2DS_2-VASc score was reliable to identify the truly low/high risk patients [6,7]. However,

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there is no validation data on the CHA_2DS_2-VASc score being used for risk stratification in patients without known AF undergoing percutaneous coronary intervention (PCI).

The aim of this study was to assess whether the CHA_2DS_2-VASc score could predict the prognosis in patients without known AF who undergo PCI.

2. Methods

2.1. Study population

This retrospective cohort study used the data for the period from August 2012 to July 2013, obtained from the SHINANO (The Shinshu Prospective Multi-center Analysis for Elderly Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention) registry. The design of the SHINANO registry has been described in detail previously [8]. In brief, the SHINANO registry is a prospective, multicenter observational registry of patients with any CHD, including stable angina, ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), and unstable angina, undergoing PCI at 16 collaborating hospitals located in the Nagano Prefecture, Japan. It has been registered with the University Hospital Medical Information Network Clinical Trials Registry which is accepted by the International Committee of Medical Journal Editors (UMIN-ID; 000010070). As an all-comer registry, there are no exclusion criteria. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients gave written informed consent before participating in this study.

Among the 1923 patients registered in the SHINANO registry, we identified 1714 patients without known AF. Patients who had no medical history for AF before revascularization were considered as patients without known AF in this study. Patients were prospectively followed for 1 year. The primary endpoint of this study was the incidence of major adverse cardiac events (MACE) including all-cause death, nonfatal MI, and ischemic stroke.

2.2. Definitions

The $CHADS_2$ score was calculated for each patient by assigning 1 point each for the presence of congestive heart failure (CHF), hypertension, age ≥75 years, or diabetes mellitus and 2 points for a history of stroke or transient ischemic attack (TIA) [1]. The CHA_2DS_2-VASc score was calculated for each patients by assigning 1 point each for the presence of heart failure (HF)/left ventricular ejection fraction <40%, hypertension, diabetes, vascular disease, age 65–74 years or female sex and 2 points for a history of stroke or age ≥75 years [5]. Study patients were divided into 3 groups based on the tertiles of CHA_2DS_2-VASc score: low, score 0–2; intermediate, score 3–4; high, score ≥5. Nonfatal MI was defined as a 2-fold or greater increase in creatine phosphokinase or troponin T levels ≥0.1 ng/ml or new Q waves in ≥2 contiguous electrocardiogram leads [9]. Ischemic stroke was defined as the presence of a new neurological deficit lasting for at least 24 h with definite evidence of infarction detected by magnetic resonance imaging or computed tomography [10]. HF was based on a previous diagnosis of HF, history of hospitalization for HF, or current treatment for HF. Diabetes was defined as HbA1C ≥6.5%, fasting plasma glucose ≥200 mg/dl, or oral hypoglycemic or insulin therapy. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg or ongoing therapy for hypertension. Dyslipidemia was defined as a serum total cholesterol concentration ≥220 mg/dl, a low-density lipoprotein cholesterol concentration ≥140 mg/dl, or current lipid-lowering therapy. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m^2 calculated using the Modification of Diet in Renal Disease formula [11]. Left ventricular ejection fraction (LVEF) was assessed with echocardiography using the Teichholz method, with LVEF ≤40% indicating left ventricular (LV) systolic dysfunction [12].

2.3. Statistical analysis

Continuous variables are presented as means ± SD, whereas dichotomous variables are described as numbers and percentages. Differences between the patients in each CHA_2DS_2-VASc score group were compared using the chi-square test for categorical variables and Student's *t* tests or Wilcoxon rank–sum tests, as appropriate, for continuous variables. The Kaplan–Meier method was used to assess cumulative mortality or morbidity in the study population. The log–rank test was used to compare survival curves. Multivariate Cox regression was performed to identify independent predictors of MACE in each CHA_2DS_2-VASc score group. Variables significantly associated with MACE were entered into the multivariate model. Receiver operating characteristics (ROC) were used to compare the performance and predictive accuracy of CHA_2DS_2-VASc score to $CHADS_2$ score for MACE [13]. Statistical analysis was performed using the Statistical Package for Social Sciences, version 21 (SPSS Inc., Chicago, IL, USA) software and statistical package ZER (version 1.27), which is a modified version of R commander (version 1.6-3) including statistical functions [14]. A $p < 0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline characteristics

Out of 1714 patients, 1632 (95.2%) completed 1 year of follow-up. Baseline characteristics of the study patients are shown in Table 1. The mean age of our cohort was 70 ± 11 years. Among the subjects, 22.9% were female, 71.2% had hypertension, 60.4% had dyslipidemia, 37% had diabetes mellitus, 40.8% had CKD, 25.3% had a previous MI, 10.9% had history of HF, 8.3% had a previous stroke, and 8.3% had LV dysfunction. Regarding lesion characteristics, 54.4% of lesions were due to acute coronary syndrome (ACS) and 89.2% were *de novo* lesions. Patients with a high (≥5) CHA_2DS_2-VASc score were more likely to be older and to have more comorbidities, including hypertension, diabetes, CKD and LV dysfunction, compared to patients with intermediate (3–4) or low (0–2) CHA_2DS_2-VASc scores. Mean SYNTAX score in overall population was categorized into low SYNTAX group. Patients with a high CHA_2DS_2-VASc score had higher SYNTAX score than those with low or intermediate CHA_2DS_2-VASc scores.

3.2. Incidence of MACE in overall population

During the follow-up period, the cumulative incidence of MACE was 8.1% ($n = 139$) for the entire study population, including 82 cases of all-cause death, 35 cases of nonfatal MI, and 22 cases of ischemic stroke. The incidence of MACE was significantly higher in patients with a high (≥5) CHA_2DS_2-VASc score compared to those with an intermediate (3–4) or low (0–2) CHA_2DS_2-VASc score (14.6% vs. 6.8% vs. 5.3%, $p < 0.001$) (Fig. 1). The details of MACE were also shown in Fig. 1. As CHA_2DS_2-VASc score increased, the incidence of all-cause death and stroke was rising. On the other hand, this trend was not found in the incidence of myocardial infarction.

To assess the relationship between MACE and CHA_2DS_2-VASc score, we performed Kaplan–Meier analysis, which revealed that patients with a high CHA_2DS_2-VASc score had a significantly higher incidence of MACE compared to patients with an intermediate or low CHA_2DS_2-VASc score (14.6% vs. 6.8% vs. 5.3%, log–rank $p < 0.001$), as shown in Fig. 2. Multivariate Cox regression analysis was performed to identify specific predictors of MACE in the study population. After adjusting for

Table 1
Baseline characteristics stratified by CHA_2DS_2-VASc score.

Variables	Overall ($n = 1714$)	Score 0–2 ($n = 643$)	Score 3–4 ($n = 659$)	Score ≥5 ($n = 412$)	*p*
Age (years)	69.9 ± 11.1	61.7 ± 9.0	71.7 ± 8.9	80.0 ± 6.8	<0.001
Female	394 (22.9%)	48 (7.4%)	142 (21.5%)	204 (49.5%)	<0.001
Body mass index (kg/m^2)	23.8 ± 6.6	23.9 ± 4.2	24.4 ± 9.2	22.7 ± 3.9	<0.001
Hypertension	1220 (71.2%)	329 (51.2%)	519 (78.8%)	372 (90.3%)	<0.001
Dyslipidemia	1035 (60.4%)	391 (60.8%)	398 (60.4%)	246 (59.7%)	<0.001
Low-density lipoprotein cholesterol (mg/dl)	109.7 ± 37.1	119.4 ± 37.5	106.2 ± 33.9	99.9 ± 33.2	<0.001
High-density lipoprotein cholesterol (mg/dl)	48.0 ± 14.6	47.6 ± 12.6	47.8 ± 14.6	49.0 ± 14.9	0.370
Diabetes mellitus	635 (37.0%)	125 (19.4%)	293 (44.5%)	217 (52.7%)	<0.001
Hemoglobin A_{1C} (%)	6.4 ± 5.9	6.2 ± 2.3	6.3 ± 1.1	7.4 ± 11.5	<0.001
Current smoker	882 (51.5%)	408 (63.4%)	328 (49.8%)	146 (35.4%)	<0.001
Estimated glomerular filtration rate (ml/min/1.73 m^2)	62.8 ± 23.5	71.0 ± 20.9	61.2 ± 23.8	52.4 ± 21.7	<0.001
Chronic kidney disease	710 (41.4%)	168 (26.1%)	284 (43.1%)	258 (62.6%)	<0.001
Hemoglobin (g/dl)	14.0 ± 6.3	15.0 ± 7.3	14.0 ± 6.6	12.6 ± 2.4	<0.001
Left ventricular ejection fraction at discharge (%)	60.3 ± 16.5	62.0 ± 11.0	60.8 ± 13.7	56.9 ± 15.8	<0.001
Left ventricular dysfunction	142 (8.3%)	17 (2.6%)	56 (8.5%)	69 (16.7%)	<0.001
Medical history					
Cerebrovascular disease	142 (8.3%)	1 (0.0%)	33 (5.0%)	108 (26.2%)	<0.001
Prior coronary artery bypass grafting	132 (7.8%)	29 (4.5%)	50 (7.6%)	53 (12.9%)	<0.001
History of heart failure	186 (10.9%)	15 (2.3%)	66 (10.0%)	105 (25.5%)	<0.001
Acute coronary syndrome on admission	779 (55.4%)	358 (55.7%)	266 (40.4%)	157 (38.1%)	<0.001
De novo lesion	1529 (89.2%)	593 (92.2%)	583 (88.4%)	353 (85.7%)	0.004
In-stent restenosis of drug-eluting stent	75 (4.4%)	22 (3.4%)	37 (5.6%)	16 (3.9%)	0.130
In-stent restenosis of bare metal stent	104 (6.1%)	28 (4.4%)	37 (5.6%)	39 (9.5%)	0.003
Calcification lesion	483 (28.2%)	122 (18.9%)	198 (30.0%)	163 (39.6%)	<0.001
Bifurcation lesion	450 (26.3%)	166 (25.8%)	173 (26.3%)	111 (26.9%)	0.935
Ostial lesion	127 (7.4%)	36 (5.6%)	51 (7.7%)	40 (9.7%)	0.044
Lesion distribution					
Left anterior descending artery	807 (47.1%)	315 (48.9%)	301 (45.7%)	191 (46.4%)	0.593
Left circumflex artery	325 (18.9%)	114 (17.7%)	132 (20.0%)	79 (19.2%)	0.500
Right coronary artery	632 (36.8%)	237 (36.9%)	243 (36.9%)	152 (36.8%)	0.968
Left main artery	40 (2.3%)	14 (2.2%)	11 (1.7%)	15 (3.6%)	0.101
Bypass graft (saphenous vein graft or internal mammary artery)	5 (0.0%)	1 (0.0%)	4 (1.0%)	0 (0.0%)	0.144
Multi-vessel disease	677 (39.4%)	213 (33.1%)	269 (40.8%)	195 (47.3%)	<0.001
SYNTAX score	12.7 ± 8.7	11.8 ± 8.5	12.7 ± 8.3	14.2 ± 9.4	0.004
Medication at discharge					
Aspirin	1644 (959.9%)	622 (96.7%)	636 (96.5%)	386 (93.7%)	0.271
Thienopyridines	1533 (89.4%)	587 (91.2%)	599 (90.9%)	347 (84.2%)	0.004
Statins	1221 (71.2%)	492 (76.5%)	461 (69.9%)	268 (65.0%)	<0.001
Angiotensin-converting enzyme inhibitors	531 (30.9%)	245 (38.1%)	178 (27.0%)	108 (26.2%)	<0.001
Angiotensin receptor blockers	615 (35.9%)	170 (26.4%)	279 (42.3%)	166 (40.3%)	<0.001
Beta-blockers	685 (39.9%)	248 (38.7%)	266 (40.4%)	171 (41.5%)	0.527
Warfarin	106 (6.2%)	35 (5.4%)	42 (6.4%)	29 (7.0%)	0.525

Data are shown as mean ± SD or as *n* (percentages).

a presence of CKD, an administration of aspirin at discharge, administration of statins at discharge and ACS, CHA_2DS_2-VASc score was an independent predictor of MACE (hazard ratio [HR] 1.26, 95% confidence interval [CI] 1.15–1.39, $p < 0.001$) (Table 2).

3.3. Comparison of the prognostic significance between CHA_2DS_2-VASc and $CHADS_2$ score

The $CHADS_2$ score was also evaluated whether it could be an independent predictor of MACE in another model using multivariate Cox-regression analysis. After adjusting gender, presence of CKD, LV dysfunction, multiple coronary artery disease, and ACS, $CHADS_2$ score was an independent predictor of MACE (HR 1.18, 95% CI 1.10–1.38, $p = 0.043$).

To compare the predictive accuracy of the CHA_2DS_2-VASc versus the $CHADS_2$ score, we described two ROC curves of CHA_2DS_2-VASc and $CHADS_2$ score, and then, we compared two areas under the ROC curve (AUC), shown in Fig. 3. The respective C-statistics for the CHA_2DS_2-VASc score and $CHADS_2$ score were 0.64 and 0.59 ($p < 0.05$).

4. Discussion

In the present study, patients with CHD but no known AF and a CHA_2DS_2-VASc score ≥5 had a significantly higher incidence of MACE compared to those who with a CHA_2DS_2-VASc score <5. Our results indicate that the CHA_2DS_2-VASc score can be used to identify high-risk patients undergoing PCI for CHD, even if they have not been diagnosed with AF.

The $CHADS_2$ and CHA_2DS_2-VASc score was originally developed for cardiogenic stroke risk stratification in patients with AF. It is a very simple and convenient scoring system for assessing the complexity of comorbidities in patients [1]. A higher score would represent an independent marker of poor prognosis due to cardiovascular disease in patients without known AF undergoing coronary angiography [15]. This score could be calculated with information on comorbidities which is easily obtainable from a medical questionnaire. This scoring system could be also used for patients with atherosclerotic disease. Recently, risk stratification using the $CHADS_2$ score has been validated in the patients with ACS [3,4]. However, there have no studies on using the CHA_2DS_2-VASc score for risk stratification in patients with

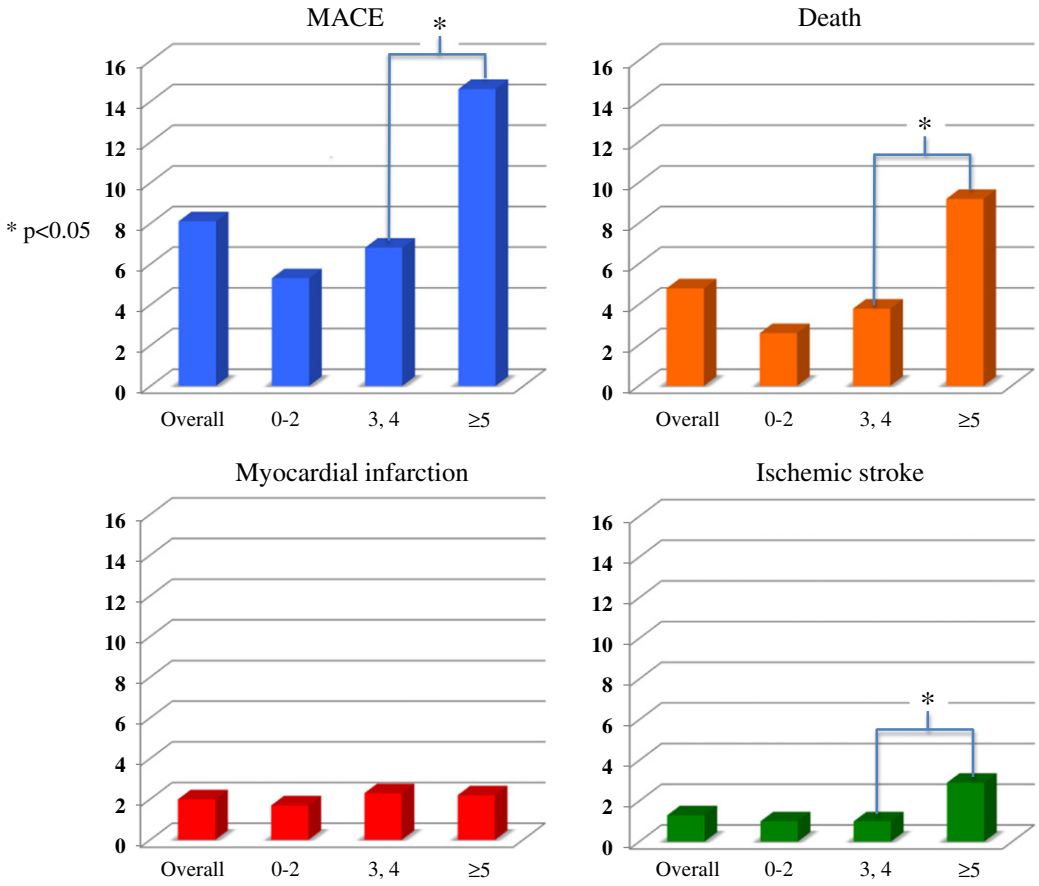

Fig. 1. The 1-year incidence of major adverse cardiac events (MACE) based on the CHA_2DS_2-VASc score 0–2, 3–4, and ≥5. The incidences of MACE, all-cause death, and stroke were significantly higher in patients with CHA_2DS_2-VASc score ≥5 than those with score 3–4 (chi-square test for linear trend $p < 0.05$). This trend was not observed between the patients with CHA_2DS_2-VASc score 0–2 and the patients with CHA_2DS_2-VASc score 3–4.

CHD, including stable angina and ACS, without known AF that are undergoing PCI.

In this study, we demonstrated that the CHA_2DS_2-VASc score had predictive value for adverse outcomes in patients with CHD undergoing PCI, even in patients with no known AF. This result was consistent with previous reports on the prognostic value of the $CHADS_2$ score in acute MI [3]. Moreover, the comparison of predictive accuracy between CHA_2DS_2-VASc and $CHADS_2$ score revealed that the CHA_2DS_2-VASc score had more powerful predictive value for MACE than that of $CHADS_2$ score. In the present study, we excluded 209 of 1923 patients (10.8%) in the SHINANO registry who had documented AF. In general, no more than 20% of patients who require PCI have concomitant AF [16]. The proportion of AF in the SHINANO registry was similar to that in recent statement; therefore, our results may be representative of the general population.

Each of the components of the CHA_2DS_2-VASc score has been reported as an independent predictor of adverse outcomes in the general population; this was one reason why there was an association between the CHA_2DS_2-VASc score and MACE in our study cohort. In developed countries, the prevalence of HF is approximately 1% to 2%, but rises to over 10% among individuals 70 years or older [17]. Before 1990, 60% to 70% of patients with HF died within 5 years of diagnosis in many countries

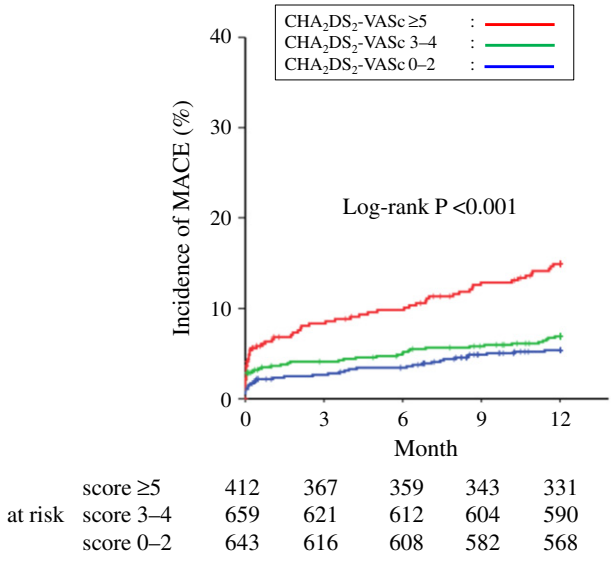

Fig. 2. Kaplan–Meier analysis of major adverse cardiac events (MACE) by CHA_2DS_2-VASc score in the overall study population. In patients with a CHA_2DS_2-VASc score ≥5, the incidence of MACE was significantly higher than in those with a CHA_2DS_2-VASc score of 3–4 or 0–2 (14.6% vs. 6.8% vs. 5.3%, log–rank $p < 0.001$).

Table 2
Multivariate analysis of MACE in the overall study population.

Variable	HR	95% CI	*p*
Estimated GFR	0.99	0.98–0.99	0.011
Acute coronary syndrome	1.69	1.18–2.42	0.004
Administration of aspirin	0.41	0.20–0.86	0.017
Administration of statin	0.73	0.50–1.07	0.101
CHA_2DS_2-VASc score	1.26	1.15–1.39	<0.001

The model included CHA_2DS_2-VASc score, an estimate glomerular filtration rate (ml/min/1.73 m^2), acute coronary syndrome on admission, an administration of aspirin at discharge, and an administration of statin at discharge.
MACE, major adverse cardiac event; HR, hazard ratio; CI, confidence interval.

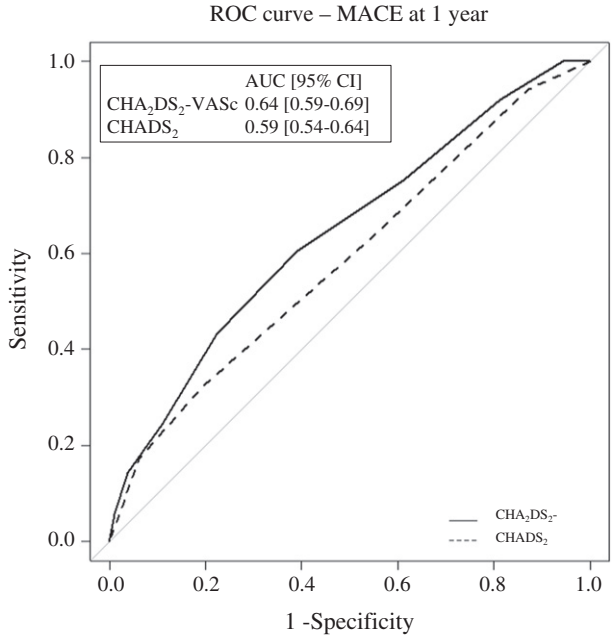

Fig. 3. Receiver operating characteristic (ROC) curves for $CHADS_2$ and CHA_2DS_2-VASc score. The predictive accuracy of CHA_2DS_2-VASc score was better than the $CHADS_2$ score ($p < 0.05$). AUC, area-under-the-curve, CI, confidence interval.

[18\]. The recent development of effective treatment has decreased HF morality, but the high incidence of mortality in HF remains an issue of concern [19]. The proportion of hypertension in the general population appears to be approximately 30% to 45% and increases with age [20]. A large number of observational studies have demonstrated an independent continuous relationship between blood pressure and the incidence of several cardiovascular events (stroke, MI, and sudden death) in all age groups and all ethnic groups [21]. Elderly patients potentially have an increased risk of mortality; older age has been reported as an independent predictor of atherosclerosis and cardiovascular events [22]. Both diabetes mellitus and disorder of glucose metabolic are risk factors for cardiovascular disease. High 2 h post-load plasma glucose predicts all-cause and cardiovascular disease mortality after adjusting for other major cardiovascular risk factors. There is a high reported absolute risk of MI or vascular death after ischemic stroke [23,24]. In recent study, patients with atherosclerotic disease are at increased risk of ischemic events in systemic vascular beds, including cardiovascular death, MI or stroke. Moreover, these event rates increased with the symptomatic vascular disease location [25]. Sex disparity in survival has been documented in several studies and women have higher mortality than men in CHD [26].

The clinical benefit of the CHA_2DS_2-VASc score in risk stratification for patients undergoing PCI is its simplicity. Only simple addition is needed to calculate CHA_2DS_2-VASc score without complex equations. We could stratify each patient undergoing PCI based on the CHA_2DS_2-VASc score, especially patients with a CHA_2DS_2-VASc score ≥ 5, which is considered high-risk.

There were several limitations in this study. First, the identification of patients without known AF was based on past medical records, medical questionnaires, and electrocardiogram monitoring during hospitalization. We did not assess the incidence of AF by ambulatory electrocardiography during the follow-up period. Henriksson et al. reported that the $CHADS_2$ score had an impact on all-cause mortality after stroke in patients with or without AF [2]. Therefore, our data might not change drastically if our patients were diagnosed AF during follow-up. Second, more than 75% in our population was male; therefore our results may not be applied to general population. However, since our study was based on observational registry data, we thought that this represented a real-world unselected population of patients with CHD undergoing PCI. Nevertheless, in patients undergoing PCI, the CHA_2DS_2-VASc score could provide prognostic information even if they were not known to have AF. A further longer follow-up study is required to evaluate the long-term impact of the CHA_2DS_2-VASc score in patients without known AF who undergo PCI.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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