ORIGINAL RESEARCH

Prognostic Value of the $CHADS_2$ Score for Adverse Cardiovascular Events in Coronary Artery Disease Patients Without Atrial Fibrillation—A Multi-Center Observational Cohort Study

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***Background*—**The $CHADS_2$ score has mainly been used to predict the likelihood of cerebrovascular accidents in patients with atrial fibrillation. However, increasing attention is being paid to this scoring system for risk stratification of patients with coronary artery disease. We investigated the value of the $CHADS_2$ score in predicting cardiovascular/cerebrovascular events in coronary artery disease patients without atrial fibrillation.

***Methods and Results*—**This was a multicenter, observational cohort study. The subjects had been admitted to one of the participating institutions with coronary artery disease requiring percutaneous coronary intervention. We calculated the $CHADS_2$ scores for 7082 patients (mean age, 69.7 years; males, 71.9%) without clinical evidence of atrial fibrillation. Subjects were subdivided into low- (0–1), intermediate- (2–3), and high-score (4–6) groups and followed for 1 year. The end point was a composite of cardiovascular/cerebrovascular death, nonfatal myocardial infarction, and ischemic stroke at 1-year follow-up. Rates of triple-vessel/left main trunk disease correlated positively with $CHADS_2$ score categories. $CHADS_2$ scores among single, double, and triple-vessel/left main trunk groups were 2 (1–2), 2 (1–3), and 2 (2–3), respectively ($P<0.001$). A total of 194 patients (2.8%) had a cardiovascular/cerebrovascular event, and Kaplan–Meier analysis demonstrated a significantly higher probability of cardiovascular/cerebrovascular events in proportion to a higher $CHADS_2$ score (log-rank test, $P<0.001$). Multivariate Cox hazard analysis identified $CHADS_2$ score (per 1 point) as an independent predictor of cardiovascular/cerebrovascular events (hazard ratio, 1.31; 95% CI, 1.17–1.47; $P<0.001$).

***Conclusions*—**This large cohort study indicated that the $CHADS_2$ score is useful for the prediction of cardiovascular/cerebrovascular events in coronary artery disease patients without atrial fibrillation. **(*J Am Heart Assoc*. 2017;6:e006355. DOI: 10.1161/JAHA.117.006355.)**

Key Words: cardiovascular disease risk factors • cardiovascular events • coronary artery disease • risk stratification

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An accompanying Appendix S1 is available at http://jaha.ahajournals.org/content/6/8/e006355/DC1/embed/inline-supplementary-material-1.pdf

**A complete list of the Kumamoto Intervention Conference Study (KICS) Investigators are given in Appendix S1.

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Clinical Perspective

What Is New?

- This large, cohort study first demonstrated a prognostic value of the $CHADS_2$ score in coronary artery disease patients without clinical evidence of atrial fibrillation for predicting subsequent cardiovascular/cerebrovascular events.

What Are the Clinical Implications?

- The $CHADS_2$ score is simple, widely applicable, well validated, and low cost, and it would be a useful tool for general clinicians as well as cardiologists to identify severe coronary artery disease patients with a high risk of subsequent cardiovascular/cerebrovascular events, for optimization of risk-reducing treatments.

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with substantial morbidity and mortality from thromboembolisms, which can induce stroke. The occurrence of stroke is proportional to the presence of certain risk factors.[1] The $CHADS_2$ score (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, or age ≥75 years, and 2 points each for past stroke or transient ischemic attack) has been used to evaluate the risk for ischemic stroke in AF patients in terms of intracardiac thrombogenesis, allowing tailored initiation of antithrombotic treatments for risk reduction, balancing against the risk of bleeding from long-term anticoagulation.[1–3] This score is commonly used in clinical practice to guide decisions regarding anticoagulant as well as antiplatelet therapy.[4] Recently, the CHA_2DS_2-VASc (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 75 years, or female sex, and 2 points each for age ≥75 years or past stroke/transient ischemic attack) and R_2CHADS_2 (adding 2 points for renal failure to the $CHADS_2$ score) scores were developed to improve the precision of risk stratification by including other important predictive factors. These newer scores have been reported to improve the accuracy of the $CHADS_2$ score in estimating the risk of stroke in AF patients.[5,6]

Each of the components of the $CHADS_2$ score has long been associated with ischemic stroke in patients with coronary artery disease (CAD) in large, cohort studies.[7–9] This suggests the possible utility of the score in predicting a wide range of cerebrovascular and cardiovascular diseases in the CAD population. Recently, several studies have reported on the use of $CHADS_2$'s predictive value for cardiovascular events in AF patients[10] and cerebrovascular events in non-AF patients.[11] It has been suggested that the $CHADS_2$ score might predict cardiovascular events in non-AF patients, though this has been investigated in relatively small populations or in a single-center study.[12]

The CHADS2 score is the original score to predict cerebrovascular accidents in AF patients, it is more prevalent than the CHA_2DS_2-VASc and R_2CHADS_2 scores, and, at present, the score is still described in the guideline and is in use.[13] On the other hand, the predictive value of this original score in CAD patients without AF is not fully demonstrated in a large and multicenter study. Thus, we wished to investigate the value of the original $CHADS_2$ score in predicting cardiovascular/cerebrovascular events in CAD patients without AF, in a multicenter and in a large population.

Methods

We conducted a multicenter, observational cohort study of 7082 consecutive CAD patients (mean age, 69.7 years; male, 71.9%) without clinical evidence of AF requiring percutaneous coronary intervention (PCI). They were enrolled between June 2008 and March 2011 through the KICS (Kumamoto Intervention Conference Study) registry, a physician-initiated, non-company-sponsored, multicenter registry involving 15 centers in Japan. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by each institutional ethics committee. Informed consent was obtained from all patients.

Baseline demographic data, cardiovascular risk factors, and medications on discharge were documented. We defined diabetes mellitus as symptoms of diabetes mellitus and a casual plasma glucose concentration ≥200 mg/dL, fasting plasma glucose concentration ≥126 mg/dL, 2-hour plasma glucose concentration ≥200 mg/dL from a 75-g oral glucose tolerance test, or taking medication for diabetes mellitus. Hypertension was defined as >140/90 mm Hg or taking antihypertensive medication, and dyslipidemia was defined as low-density lipoprotein ≥140 mg/dL (≥3.63 mmol/L), high-density lipoprotein <40 mg/dL (1.04 mmol/L), or triglycerides ≥150 mg/dL (≥1.7 mmol/L). We also evaluated the incremental effect of chronic kidney disease (CKD) on clinical outcome, following the recent suggestion that adding renal function to the score (R_2CHADS_2) improves stroke risk stratification in AF patients over that of $CHADS_2$.[6] CKD was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Smoking status was determined by interview. Acute coronary syndrome was defined as either an acute myocardial infarction (MI; ST-elevation MI or non-ST-elevation MI) or unstable angina pectoris. Patients with past or current intermittent claudication associated with an ankle-brachial index value of <0.9 in either leg were categorized as having peripheral arterial disease. Patients with previous ischemic stroke or transient ischemic attack were defined as having cerebrovascular disease.

The $CHADS_2$ score was calculated for each PCI patient at discharge. The previous studies to investigate the predictive value of the $CHADS_2$ score for cardiovascular events in AF patients[10] and cerebrovascular events in non-AF patients[11] adopted categories of low (0–1), intermediate (2–3), and high (4–6) scores. This categorization had been reported to have a higher value of C-statistic than that of categorization into low and high scores in the original literature of the $CHADS_2$ score.[14] In the present study, we also divided subjects according to score values into 3 subgroups similarly to describe baseline poststenting characteristics and then to evaluate the effect of higher $CHADS_2$ score on clinical outcome. We classified the severity of CAD into single-, double-, and triple-vessel or left main trunk (LMT) disease requiring PCI.

After coronary stent implantation, patients were followed prospectively at outpatient clinics in each institution. Cardiovascular and cerebrovascular events were ascertained from a review of medical records and confirmed by direct contact with the patients, their families, and physicians. The end point was a composite of cardiovascular or cerebrovascular death, nonfatal MI, and ischemic stroke at 1-year follow-up after PCI; it has been reported that patients with atherosclerotic arterial disease or at risk of atherothrombosis experience high incidence of cardiovascular events within 1 year.[15] "Cardiovascular death" was defined as death attributed to MI, congestive heart failure, or documented sudden cardiac death. We used the universal definition of MI in this study.[16] The diagnosis of ischemic stroke was based on clinical and radiological evidence of stroke. For subjects who had ≥2 cardiovascular events, only the first event was considered in the analysis.

The Shapiro–Wilk test was used to assess the normal distribution of continuous data. Continuous variables with a normal distribution are expressed as the mean (SD). The results of the $CHADS_2$ score were expressed by medians and interquartile ranges. Categorical data are presented as numbers or percentages. Differences between 2 groups were tested using Fisher's exact test or the chi-squared test for categorical variables, as appropriate. Differences in continuous variables were analyzed by the ANOVA or the Kruskal–Wallis test, as appropriate. We used the Kaplan–Meier method to estimate the cardiovascular event probabilities at 365 days and also the log-rank test to compare the distributions of survival times among groups. Cox proportional hazard models were used to calculate hazard ratios. Predictors of clinical outcome identified through univariate analysis were tested in a multivariate analysis. We selected variables of statistically significant in the univariate analyses ($P<0.05$) and to exclude variables that will cause internal correlations. The factors of age, hypertension, diabetes mellitus, cerebrovascular disease, and heart failure were components of the $CHADS_2$ score, and we thought these variables cause internal correlations with the $CHADS_2$ score variable. Estimates of the C-statistic for the risk factors were calculated after the addition of the $CHADS_2$ score and CKD factor to the risk factors of independent predictive values identified in the multivariate Cox proportional hazards regression analyses; it is generally considered C-statistic above 0.7 acceptable discriminatory power, that above 0.8 excellent discriminatory power, and that above 0.9 outstanding discriminatory power. The incremental effect of adding the $CHADS_2$ score and CKD factor or the to other risk factors in predicting future cardiovascular events was evaluated using the net reclassification improvement (NRI) as previously described.[17] Considering potential center effects, we adjusted predictive models by including center variables as dummy variables. $P<0.05$ was considered to denote statistical significance. Statistical analyses were performed using commercial software (SPSS version 22; IBM Inc, Armonk, NY).

Results

A total of 7082 CAD patients requiring PCI were recruited into this study. The $CHADS_2$ scores of the patients are shown in Figure 1. The baseline laboratory and clinical findings for the study patients according to low, intermediate, and high scores are listed in Table 1. Patients with high $CHADS_2$ scores were older; had higher rates of dyslipidemia, CKD (including hemodialysis status), past coronary artery bypass graft, peripheral arterial disease, and use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers; and lower rates of current smoking.

The left side of Figure 2A shows the distribution of triple-vessel or LMT CAD among the low, intermediate, and high $CHADS_2$ scores. The rate of triple-vessel or LMT disease

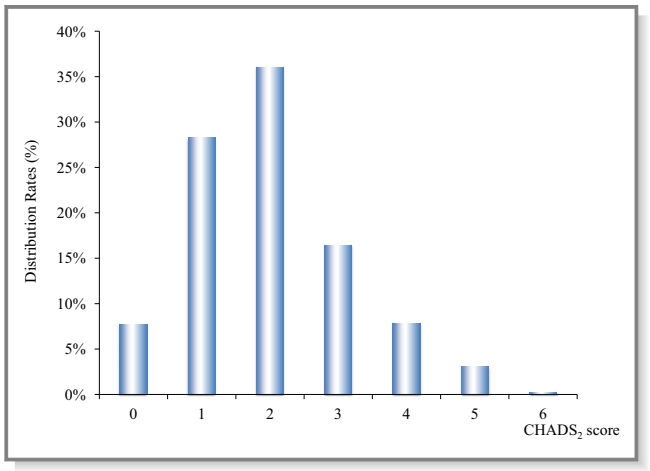

Figure 1. Distribution of $CHADS_2$ scores over the total population.

Table 1. Characteristics of the Trial Participants at Baseline According to $CHADS_2$ Score

	Total (n=7082)	0 to 1 Points (n=2555)	2 to 3 Points (n=3723)	4 to 6 Points (n=803)	*P* Value
Age, y (SD)	69.7 (11.0)	64.5 (10.0)	72.1 (10.5)	75.1 (9.2)	<0.001
Male sex, n (%)	5092 (71.9)	1996 (78.1)	2527 (67.9)	569 (70.9)	<0.001
Body mass index (SD)	23.9 (3.5)	24.0 (3.3)	24.0 (3.5)	23.5 (3.5)	0.002
Abd circumference, cm (SD)	86.6 (9.7)	86.1 (9.2)	86.8 (10.0)	86.9 (10.0)	0.087
Hypertension, n (%)	5496 (77.6)	1311 (51.3)	3413 (91.7)	772 (96.1)	<0.001
Diabetes mellitus, n (%)	3097 (43.7)	328 (12.8)	2231 (59.9)	538 (67.0)	<0.001
Dyslipidemia, n (%)	4565 (64.5)	1571 (61.5)	2455 (65.9)	539 (67.1)	<0.001
Chronic kidney disease, n (%)	3034 (42.8)	729 (28.5)	1796 (48.2)	509 (63.4)	<0.001
Hemodialysis, n (%)	365 (5.2)	87 (3.4)	207 (5.6)	71 (8.8)	<0.001
Current tobacco use, n (%)	1678 (23.7)	773 (30.3)	762 (20.5)	143 (17.8)	<0.001
Acute coronary syndrome, n (%)	3541 (50.0)	1343 (52.6)	1804 (48.5)	394 (49.1)	0.005
Previous MI, n (%)	1401 (19.8)	477 (18.7)	752 (20.2)	172 (21.4)	0.153
Past PCI, n (%)	1891 (32.4)	644 (29.7)	1040 (34.2)	207 (33.1)	0.003
Past CABG, n (%)	346 (4.9)	96 (3.8)	196 (5.3)	54 (6.7)	0.001
Peripheral arterial disease, n (%)	648 (9.2)	112 (4.4)	388 (10.4)	148 (18.4)	<0.001
Cerebrovascular disease, n (%)	986 (13.9)	0 (0)	272 (7.3)	714 (88.9)	<0.001
Recent CHF, n (%)	853 (12.0)	97 (3.8)	530 (14.2)	226 (28.1)	<0.001
Coronary lesions, n (%)					
Single lesions	3720 (52.5)	1560 (61.1)	1827 (49.1)	333 (41.5)	<0.001
Double lesions	1911 (27.0)	637 (24.9)	1054 (28.3)	220 (27.4)	0.011
Triple or LMT lesions	1449 (20.5)	357 (14.0)	842 (22.6)	250 (31.1)	<0.001
Medication on discharge, n (%)					
Statin	5410 (76.4)	2001 (78.3)	2798 (75.2)	611 (76.1)	0.016
ACE inhibitor or ARB	5075 (71.7)	1698 (66.4)	2768 (74.3)	609 (75.8)	<0.001
Beta-blocker	3290 (46.5)	1068 (41.8)	1792 (48.1)	430 (53.5)	<0.001

ACE inhibitor indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention.

positively correlated with a higher $CHADS_2$ score. The $CHADS_2$ scores among single-, double-, and triple-vessel or LMT CADs were 2 (1–2), 2 (1–3), and 2 (2–3), respectively (P<0.001; the right side).

As detailed in Table 2, a total of 194 patients (2.8%) suffered a cardiovascular or cerebrovascular event. The rates of cardiovascular events among low, intermediate, and high $CHADS_2$ score groups were 1.5%, 3.3%, and 4.9%, respectively (Figure 2B, left side). Patients with cardiovascular/cerebrovascular events had significantly higher $CHADS_2$ scores than those without events, at 2 (2–3) versus 2 (1–3; P<0.001; Figure 2B, right side). We performed a Kaplan–Meier analysis and observed that a significantly higher incidence of cardiovascular/cerebrovascular events was in proportion to a higher $CHADS_2$ score (log-rank test, P<0.001; Figure 3A). Rates of cardiovascular or cerebrovascular death and ischemic stroke were higher in proportion to $CHADS_2$ score (P<0.001; Figure 3B and 3D), respectively, but there was no significant difference in the rates of non-fatal MI among the low, intermediate, and high $CHADS_2$ score groups (P=0.331; Figure 3C). We also evaluated the occurrence of cardiovascular events during 2 periods, from discharge to 30 days and from 30 days to 1 year (Figure 4). The results of Cox proportional hazards analyses are shown in Table 3. We included the $CHADS_2$ score, body mass index, acute coronary syndrome, dyslipidemia, CKD, and peripheral arterial disease, and excluded hemodialysis, 1 vessel disease, LMT/3 vessel disease, and statin attributed to the internal correlation. Multivariate analyses identified $CHADS_2$ score (per 1 point) as an independent and significant predictor of the primary outcome (hazard ratio, 1.31; 95% CI, 1.17–1.47; P<0.001).

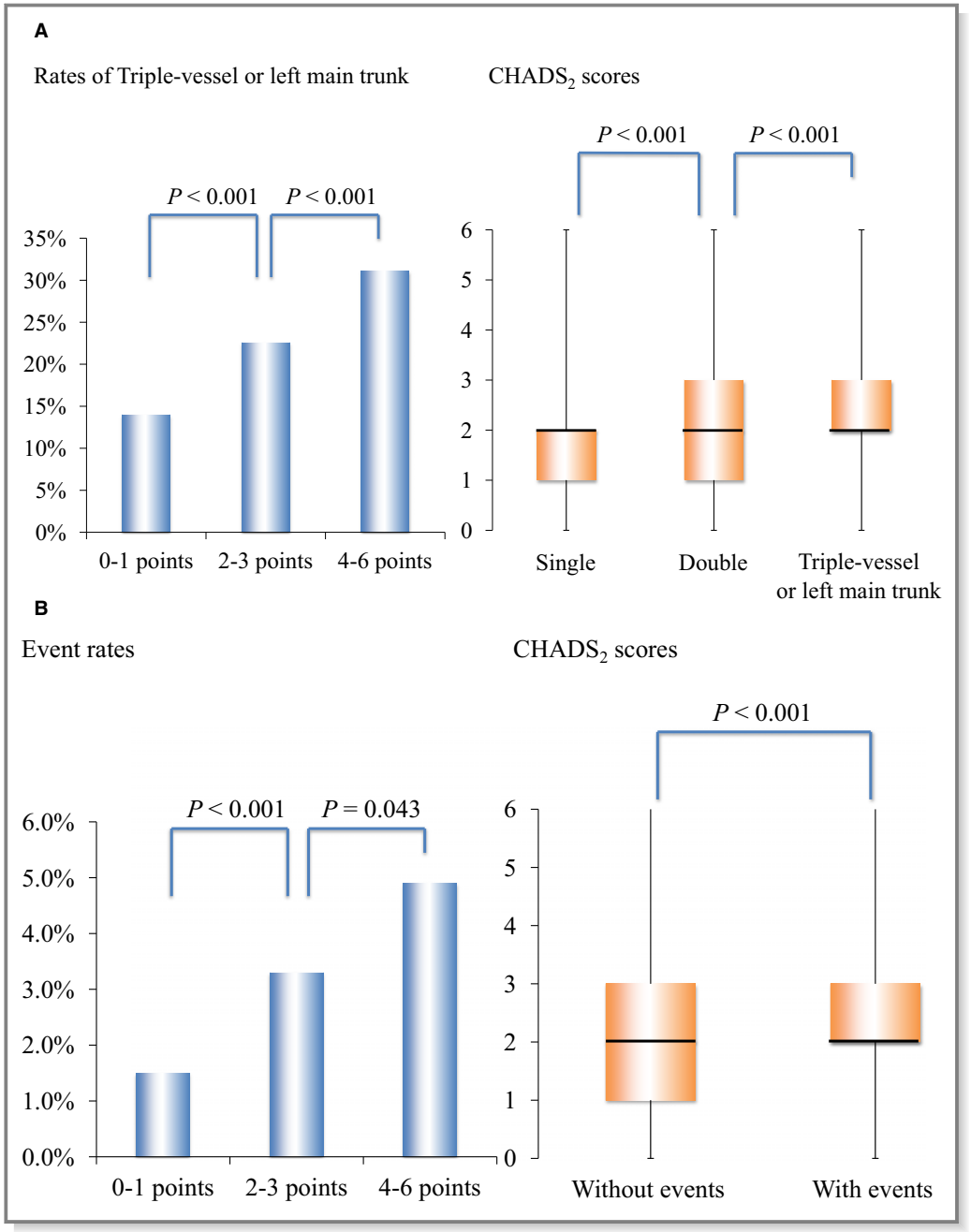

Figure 2. A, CHADS$_2$ scores and severity of CAD. The left side; rates of triple-vessel or left main trunk disease among low, intermediate, and high CHADS$_2$ scores. The right side, CHADS$_2$ scores among patients with single, double, and triple-vessel or left main trunk disease. B, CHADS$_2$ scores and rates of adverse cardiovascular events. The left side; rates of primary outcome among low, intermediate, and high CHADS$_2$ scores. The right side; CHADS$_2$ scores compared between patients with and without cardiovascular events.

From the results of the Cox proportional hazards regression analyses, we calculated the C-statistic for the predictive value of future cardiovascular events. The C-statistic of the variables, including body mass index, acute coronary syndrome, dyslipidemia, and peripheral arterial disease peripheral arterial disease, was 0.69 versus 0.72 when CHADS$_2$ score was included; the continuous NRI was 16.5% (8.7–23.4%; P<0.001). After including the CKD with these factors, we found an increase in C-statistic from 0.72 to 0.74, and the continuous NRI was 20.8% (13.0–27.6%; P<0.001).

Discussion

The main findings of this study were as follows: (1) The CHADS$_2$ score was higher in relation to the severity of CAD; (2) CAD patients with higher CHADS$_2$ score points had a

Table 2. Primary End Points by $CHADS_2$ Score During 1-Year Follow-up

Primary End Point	Total (n=6891)	Low (0–1) (n=2505)	Intermediate (2–3) (n=3615)	High (4–6) (n=771)
Total (%)	194 (2.8)	38 (1.5)	118 (3.3)	38 (4.9)
Cardiovascular death (%)	88 (1.3)	14 (0.6)	57 (1.6)	17 (2.2)
Nonfatal MI (%)	58 (0.8)	16 (0.6)	34 (0.9)	8 (1.0)
Stroke (%)	48 (0.7)	8 (0.3)	27 (0.7)	13 (1.7)

MI indicates myocardial infarction.

significantly higher probability of adverse cardiovascular/cerebrovascular events by the log-rank test; (3) multivariate Cox proportional hazards analysis showed that the $CHADS_2$ score and presence of CKD were independent and significant predictors of clinical outcome in CAD patients; and (4) predictive model improvements by significant NRIs after adding the $CHADS_2$ score and CKD status to the model of other independent predictive values.

To our knowledge, this is the largest study to examine the association of $CHADS_2$ score with severity of CAD and with future adverse cardiovascular/cerebrovascular events in CAD patients without clinical evidence of AF. The $CHADS_2$ score was originally developed for risk prediction and stratification of ischemic stroke in patients with nonvalvular AF and for guiding anticoagulant therapy.[1,2,5] The $CHADS_2$ score is also reportedly useful in the prediction of cardiovascular events in

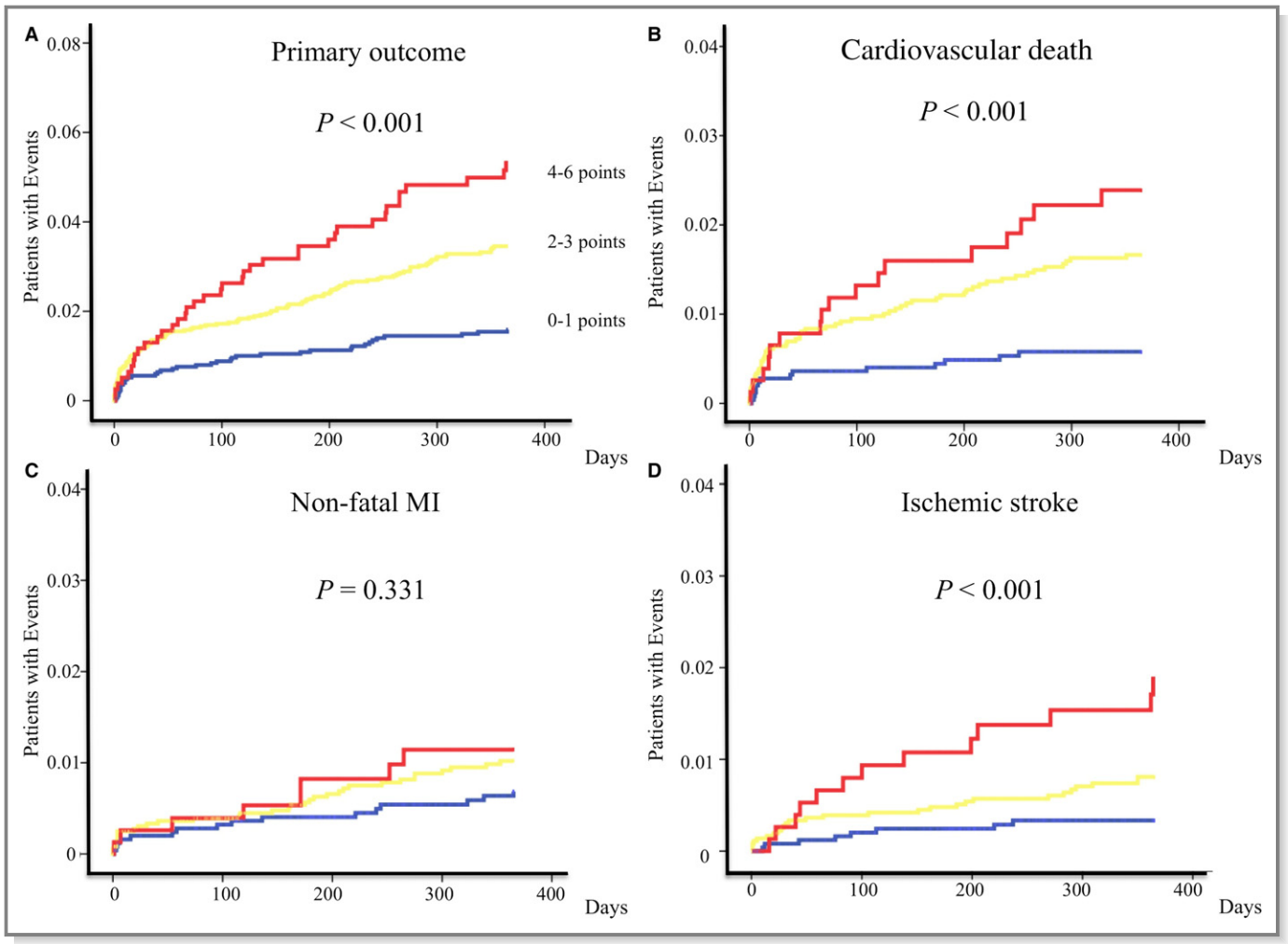

Figure 3. Kaplan–Meier analyses at 1-year follow-up. Kaplan–Meier analyses of primary outcome (A), cardiovascular or cerebrovascular death (B), nonfatal myocardial infarction (C), and ischemic stroke (D). MI indicates myocardial infarction.

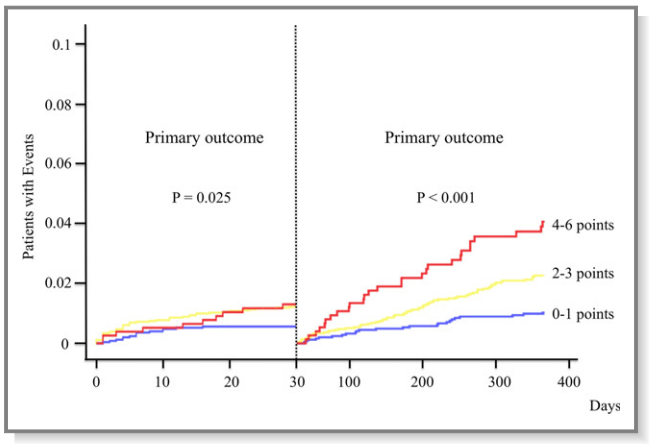

Figure 4. Kaplan–Meier analyses during 2 periods, from 30 days and from 30 days to 1 year.

AF patients[10] and of ischemic stroke in non-AF patients.[11,18] Moreover, although in a relatively small population in a single-center study, 1 report has indicated that the $CHADS_2$ score might predict adverse cardiovascular events in non-AF patients with vascular dysfunction.[19] These reports suggest that the $CHADS_2$ score has the ability to predict severe atherosclerosis and cerebrovascular and cardiovascular events in the presence or absence of AF. It would be reasonable that in this specific population in the present study, the distribution would shift to the higher $CHADS_2$ score category. Actually, however, we found that the distribution in the present study was similar to the 1 reported on in the original literature.[14] Not surprisingly, we observed high frequencies of severe CAD (triple-vessel or LMT) in our subjects, and it is well known that adverse cardiovascular events are more frequent in CAD patients with multivessel disease.[20] Indeed, in the present study, we found that CAD patients with multivessel disease had a significantly higher $CHADS_2$ score than those with single-vessel disease, and that the $CHADS_2$ score was a predictor of future cardiovascular/cerebrovascular events in CAD patients by 2 metrics: the C statistic derived from multivariate Cox proportional hazards models, and the NRI. Thus, our results support and demonstrate previous reports in a large population in a multicenter study. We also evaluated the occurrence of cardiovascular events during 2 periods, from discharge to 30 days and from 30 days to 1 year, and found that the impact of the $CHADS_2$ score on clinical outcome are clearer after 30 days within 1-year follow-up. Within 30 days, many other factors such as medications and intervention results might affect the outcome, and the impact of the $CHADS_2$ score is more significant in the chronic phase.

A recent study in high-risk patients (CAD, ischemic stroke, and diabetes mellitus) without AF reported that the $CHADS_2$ score might have clinical applications for prediction of cardiovascular/cerebrovascular events, and that the $CHADS_2$ score was associated with other biological markers of vascular injury, such as brachial flow-mediated dilation, carotid intimal thickness, and pulse wave velocity.[19] It has been reported that impaired vascular endothelial function assessed by flow-mediated dilation is related to the severity of CAD,[21] and that endothelial dysfunction may predict cardiovascular events in patients with CAD.[22] Impaired vascular endothelial function generally triggers the platelet adhesion and aggregation and fibrin formation that play a critical role in systemic hypercoagulability.[23] Vascular endothelial dysfunction is associated with cardiovascular risk factors[24,25] and is 1 of the key agents of not only coronary atherosclerosis/plaque vulnerability, but also other cardiovascular complications such as vascular remodeling.[26] Chan et al previously reported the significant association of the $CHADS_2$ score with vascular endothelial function assessed by flow-mediated dilation in non-AF patients.[19] Even in the absence of AF, patients with heart failure, hypertension, older age, and diabetes mellitus have elevated markers of endothelial dysfunction and hypercoagulability,[24,27–29] indicating that platelet activation might be attributed to underlying risk factors other than AF. Therefore, the combined factors of the $CHADS_2$ score can predict adverse events in the absence of AF. In this study, we further evaluated subjects' peripheral endothelial function in 698 CAD patients without AF using a reactive hyperemia-peripheral arterial tonometry system and found that CAD patients with higher $CHADS_2$ score had significantly impaired peripheral endothelial function ($P<0.001$, data not shown). This suggests that more-careful observation and intensive risk reduction treatment might be needed to treat CAD patients with a high $CHADS_2$ score.

A recent study has reported that the R_2CHADS_2 score, in which the presence of CKD is factored into the original $CHADS_2$ score, improves risk stratification for stroke occurrence in AF patients.[6] In our study, adding CKD status to the other predictors of clinical outcome resulted in an improvement in prognostic ability. It is well known that renal dysfunction is associated with cardiovascular events, and we previously reported that peripheral endothelial function was impaired in CKD patients and was associated with cardiovascular events.[28] Renal dysfunction–induced hypertension and vascular calcification, leading to increased cardiac afterload, were reported to be associated with cardiovascular events in CKD patients partially through associated lipid disorders, oxidative stress, and abnormal levels of homocysteine and fibrinogen,[30] suggesting that the R_2CHADS_2 score is more accurate than the $CHADS_2$ score in prediction of subsequent cardiovascular/cerebrovascular events in CAD patients. Further investigation on the newer scores, such as CHA_2DS_2-VASc and R_2CHADS_2 scores, will be required in CAD patients without AF.

Table 3. Cox Proportional Hazards Regression Analyses for Clinical Outcome

	Univariate Regression			Multivariate Regression		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
$CHADS_2$ score	1.39	1.25 to 1.55	<0.001	1.31	1.17 to 1.47	<0.001
Age	1.03	1.02 to 1.05	<0.001			
Male sex	1.01	0.74 to 1.39	0.94			
BMI	0.94	0.90 to 0.98	0.002	0.97	0.93 to 1.01	0.17
AC	0.99	0.97 to 1.01	0.34			
ACS	2.44	1.79 to 3.31	<0.001	2.20	1.60 to 3.04	<0.001
Hypertension	1.02	0.73 to 1.44	0.89			
Diabetes mellitus	1.17	0.89 to 1.55	0.27			
Dyslipidemia	0.59	0.45 to 0.79	<0.001	0.67	0.50 to 0.91	0.009
Current smoking	1.24	0.91 to 1.70	0.17			
CKD	2.34	1.75 to 3.13	<0.001	1.87	1.37 to 2.54	<0.001
Hemodialysis	2.06	1.28 to 3.30	0.003			
PAD	1.79	1.20 to 2.65	0.004	1.88	1.24 to 2.84	0.003
CVD	1.81	1.29 to 2.54	0.001			
HF	3.05	2.23 to 4.18	<0.001			
Past PCI	0.77	0.55 to 1.07	0.11			
Past CABG	1.14	0.62 to 2.09	0.67			
Previous MI	0.87	0.61 to 1.26	0.47			
1 VD	0.75	0.57 to 1.00	0.046			
LMT or 3 VD	1.74	1.28 to 2.36	<0.001			
Statin	0.58	0.43 to 0.78	<0.001			
Beta-blocker	0.94	0.71 to 1.25	0.67			
ACE-I/ARB	1.33	0.95 to 1.86	0.095			

AC indicates abdominal circumference; ACE-I, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CVD, cerebrovascular disease; HF, heart failure; HR, hazards ratio; LMT, left main trunk; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; VD, vessel disease.

Perspectives

Although the $CHADS_2$ score was originally developed to predict the risk of stroke in AF patients, accumulating evidence suggests that it works irrespective of the presence or absence of AF. Each of the components of the $CHADS_2$ score is simple and calculating the score is easy in clinical practice and is widely applicable, well validated, and low cost. If this score predicts subsequent cardiovascular events in CAD patients, it would be a useful tool for general clinicians as well as cardiologists. Our large, cohort study first demonstrated the predictive and prognostic values of the $CHADS_2$ score in CAD without AF to identify severe CAD patients with a high risk of subsequent cardiovascular/cerebrovascular events, for optimization of risk-reducing treatments, and found that adding CKD status further honed its accuracy. Our understanding of CAD is moving from simple stenoses to the large role of endothelial dysfunction as the final common pathway of many cardiovascular/cerebrovascular events.

Study Limitations

This study has some limitations. First, it included only Japanese patients. Thus, our results might not be applicable to different ethnic populations all over the world. Second, we enrolled CAD patients without clinical evidence of AF, but we cannot deny the possibility that the study population included those with the potential existence of asymptomatic paroxysmal AF; also, the follow-up at the outpatient clinic was performed at each center and we could not fully monitor cardiac rhythm to exclude AF. Third, we evaluated the severity of CAD only by the number of diseased coronary arteries and did not use other risk markers. Fourth, the follow-up was performed at each center and the information of visits interval

is lacking. This lack of information might affect the results in the present study.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

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