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Additive Prognostic Value of Carotid Plaque Score to Enhance the Age, Creatinine, and Ejection Fraction Score in Patients with Acute Coronary Syndrome

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Aim: To assess whether combining measurements obtained from carotid ultrasonography in addition to the age, creatinine, and ejection fraction (ACEF) score would improve the predictive ability of outcome in patients with acute coronary syndrome (ACS).

Methods: We examined 264 patients with ACS (194 men; mean age: 68±11 years) who underwent percutaneous coronary intervention. The carotid plaque score (cPS) and intima−media thickness (cIMT) were determined by carotid ultrasonography. The modified ACEF score was calculated using the following formula: (age/left ventricular ejection fraction) +1 point for every 10 mL/min reduction in creatinine clearance below 60 mL/min per 1.73 m^2. The endpoint of this study was major adverse cardiovascular and cerebrovascular events (MACEs), defined as all-cause death, myocardial infarction, stoke, and target vessel revascularization.

Results: During the median 4-year follow-up, there were 121 incidents of MACEs. Multivariate Cox proportional hazard regression analysis revealed that cPS ≥9.8 (hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.01−2.31) and ACEF score ≥1.20 (HR, 1.62; 95% CI, 1.11−2.39) were significantly associated with MACEs, whereas cIMT was not. When the new combined risk score was calculated by multiplying the cPS by the modified ACEF score, the freedom from MACEs at 5 years was 71% and 31% for the lower and higher scores, respectively ($p<0.001$). The area under the receiver-operating characteristic curve for MACEs for the ACEF score, cPS, and combined risk score were 0.65, 0.66, and 0.71, respectively ($p<0.05$).

Conclusion: The cPS offers an incremental predictive value when combined to the simple ACEF score in ACS.

Key words: Acute coronary syndrome, Carotid ultrasonography, Risk stratification

Introduction

Although the patient prognosis after acute coronary syndrome (ACS) has improved since the introduction of primary percutaneous coronary intervention (PCI), as well as statin and antithrombotic therapy, risk stratification in these patients remains one of the major challenges for physicians[1-3]. Age, ejection fraction, and renal function have been identified as powerful predictors of ACS in patients after myocardial infarction[4-6]. Under these conditions, age, creatinine, and ejection fraction (ACEF) score has been reported as a simple and useful clinical tool for predicting outcome in patients with ACS[7-9]; however, this clinical risk model does not contain anatomical characteristics that reflect the severity of coronary artery disease and subsequent outcome.

Non-invasive determination of carotid intima-media thickness (cIMT) using high-resolution B-mode ultrasonography has been reported in the diagnosis of subclinical carotid atherosclerosis as both a surrogate marker of coronary atherosclerosis and as a predictor

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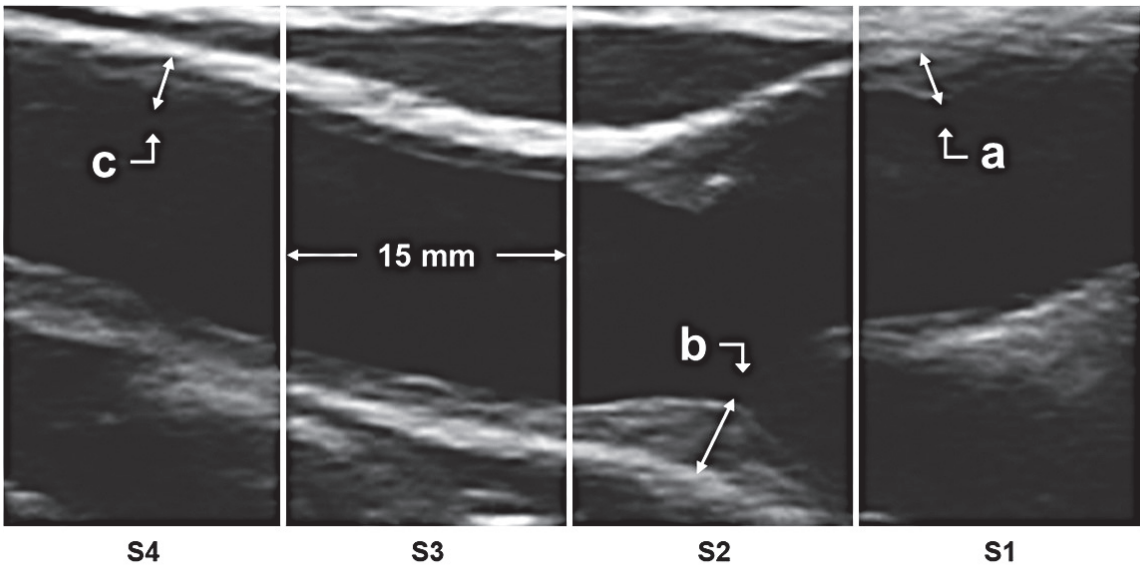

Fig. 1. Measurement of the carotid plaque score

The plaque score was computed by summing the maximum thickness (millimeters) of the plaques in each segment on both sides (a + b + c + contralateral plaques). S1, region of the ICA < 15 mm distal to its bifurcation from the CCA; S2, region of the ICA and CCA < 15 mm proximal to the bifurcation; S3, region of the CCA > 15 mm and < 30 mm proximal to the bifurcation; S4, region of the CCA > 30 mm proximal to the bifurcation below the flow divider. The length of each of the plaques was not considered in determining the plaque score. ICA, internal carotid artery; CCA, common carotid artery.

of future cardiovascular events[10-15]. In addition to the robust association between coronary angiographic severity and prognosis in patients with ACS[16, 17], a recent study suggested that the carotid plaque score (cPS) is a more reliable parameter in predicting the severity of coronary artery disease compared with cIMT[10]. Since previous studies of angiographic risk score have demonstrated the importance of combining clinical and anatomical factors for risk stratification in patients undergoing PCI[18-21], we hypothesized that combining measurements obtained from carotid ultrasonography in addition to the simple ACEF score would improve the predictive ability of outcome in patients with ACS.

Aim

The aim of this study was to assess the incremental prognostic value of cPS and cIMT in patients with ACS.

Methods

Study Population

This was a single center retrospective study. From November 2006 to May 2015, 354 consecutive patients with ACS who underwent PCI were analyzed. All PCI procedures were performed using standard techniques. During the study period, 90 patients with ACS who did not undergo examination of carotid ultrasonography were excluded. Finally, 264 patients were included for analysis. The median duration from the date of PCI to carotid ultrasonography was 9 days (interquartile range: 5 to 16 days). Our study complied with the Declaration of Helsinki and was approved by the local ethics committee with respect to the use of the clinical data.

Definitions

We defined ACS as ST-segment elevated myocardial infarction, non-ST-segment elevated myocardial infarction, or unstable angina pectoris. Myocardial infarction was defined as an increase in serum creatine kinase of 2 times the upper limit of the normal range with elevated muscle-brain fraction[22]. Patients with ST-segment elevated myocardial infarction exhibited ST-segment elevation of > 1 mm on 2 or more contiguous leads. Patients with non-ST-segment elevated myocardial infarction exhibited elevated cardiac enzymes, as noted above, without ST-segment elevation on the ECG. Unstable angina pectoris was defined by the following criteria: presence of typical chest discomfort lasting at least 5 min and occurring within 96 h of (or during) hospital admission, and having an unstable pattern of pain, consisting of either resting pain, new onset, severe or frequent angina, or accelerating angina[23].

Table 1. Baseline clinical characteristics

Variable	All (n=264)	cPS		P value	cIMT		P value
		Higher (≥9.8) (n=133)	Lower (<9.8) (n=131)		Higher (≥0.8 mm) (n=142)	Lower (<0.8 mm) (n=122)	
Age, years	68±11	71±9	64±12	<0.001	71±10	65±11	<0.001
Male gender, n (%)	194 (73)	100 (75)	94 (72)	0.53	107 (75)	87 (71)	0.46
Clinical presentation				0.81			0.93
STEMI, n (%)	126 (48)	61 (46)	65 (50)		68 (48)	58 (48)	
NSTEMI, n (%)	43 (16)	23 (17)	20 (15)		22 (15)	21 (17)	
UAP, n (%)	95 (36)	49 (37)	46 (35)		52 (37)	43 (35)	
Hypertension, n (%)	181 (69)	101 (76)	80 (61)	<0.05	102 (72)	79 (65)	0.22
Diabetes mellitus, n (%)	101 (38)	59 (44)	42 (32)	<0.05	59 (42)	42 (34)	0.23
Dyslipidemia, n (%)	114 (43)	63 (47)	51 (39)	0.17	65 (46)	49 (40)	0.36
Current smoker, n (%)	115 (44)	59 (44)	56 (43)	0.79	67 (47)	48 (39)	0.20
Previous MI, n (%)	27 (10)	15 (11)	12 (9)	0.57	17 (12)	10 (8)	0.31
Previous stroke, n (%)	35 (13)	26 (20)	9 (7)	<0.05	26 (18)	9 (7)	<0.05
CrCL (mL/min)	71±40	61±34	82±42	<0.001	68±39	75±41	0.20
Left ventricular EF (%)	58±14	56±14	59±13	0.13	56±14	59±13	0.17
Medication during hospital stay							
ACE inhibitor or ARB, n (%)	212 (80)	108 (81)	104 (79)	0.71	114 (80)	98 (80)	0.99
β-blocker, n (%)	144 (55)	77 (58)	67 (51)	0.27	81 (57)	63 (52)	0.38
Statin, n (%)	223 (84)	110 (83)	113 (86)	0.43	122 (86)	101 (83)	0.48

Values are expressed as n (%) or mean±standard deviation.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CrCL, creatinine clearance; cIMT, carotid intima-media thickness; cPS, carotid plaque score; EF, ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevated myocardial infarction; NSTEMI, Non-ST-segment elevated myocardial infarction; UAP, unstable angina pectoris.

The presence of coronary artery stenosis was defined as a lumen diameter stenosis ≥50% in a major coronary artery[24]. Each patient was classified into one of the following groups based on the numbers of diseased vessels: 1-vessel disease, 2-vessel disease, 3-vessel disease (patients with disease in 3 vessels or left main trunk disease). Multivessel disease was defined as ≥50% luminal narrowing in more than 2-vessels or in the left main trunk. Hypertension was defined as a blood pressure ≥140/90 mmHg or requiring treatment with antihypertensive medications. Diabetes mellitus was defined as HbA1c ≥6.5%, plasma glucose ≥200 mg/dL, or requiring treatment with insulin or hypoglycemic agents. Dyslipidemia was defined as a serum total cholesterol concentration ≥220 mg/dL, a low-density lipoprotein-cholesterol concentration ≥140 mg/dL, or currently requiring treatment with lipid-lowering therapy. Standard transthoracic M-mode and 2-dimensional echocardiographic studies were performed within a week after experiencing an ACS. Left ventricular ejection fraction was calculated by the Teichholz method and by the modified Simpson's method when left ventricular dilatation or a regional reduction of the left ventricular wall motion occurred.

The ACEF score was computed as follows: (age/left ventricular ejection fraction) +1 if serum creatinine value was >2 mg/dL[7]. The modified ACEF score was calculated using the following formula: (age/left ventricular ejection fraction) +1 point for every 10 mL/min reduction in creatinine clearance below 60 mL/min per 1.73 m^2 (up to a maximum of 6 points)[18]. Creatinine clearance was calculated using the Cockcroft–Gault equation[25]. In all patients, peripheral venous blood samples for laboratory analysis were drawn at the time of presentation before the patients were transferred to the catheter laboratory.

Assessment of Carotid Ultrasonography

Carotid ultrasonography parameters were measured using ultrasound system (Aplio, Toshiba Medical Systems, Tokyo, Japan) with a 7.5-MHz transducer, by trained sonographers who were blinded to the clinical data. The cIMT was recorded during the examination, as described previously[26]. In brief, cIMT from the right and left side was measured from the far wall; the location of which was identified as the vertical distance from the leading edge of the first to the second echogenic line. Three independent cIMT determinations were measured in the walls at the site of greatest thickness of each common carotid artery, and these

Table 2. Angiographic and procedural characteristics

Variable	All ($n=264$)	cPS		*P* value	cIMT		*P* value
		Higher (≥9.8) ($n=133$)	Lower (<9.8) ($n=131$)		Higher (≥0.8 mm) ($n=142$)	Lower (<0.8mm) ($n=122$)	
Culprit lesion location							
Left main, n (%)	9 (3)	5 (4)	4 (3)	0.75	6 (4)	3 (2)	0.42
Left anterior descending, n (%)	118 (45)	51 (38)	67 (51)	<0.05	56 (39)	62 (51)	0.06
Left circumflex, n (%)	42 (16)	22 (17)	20 (15)	0.78	23 (16)	19 (16)	0.89
Right, n (%)	96 (36)	54 (41)	42 (32)	0.15	59 (42)	37 (30)	0.06
Graft vessel, n (%)	4 (2)	4 (3)	0 (0)	<0.05	2 (1)	2 (2)	0.88
Multivessel disease, n (%)	154 (58)	95 (71)	59 (45)	<0.001	94 (66)	60 (49)	<0.05
Pre-PCI TIMI flow grade 0 or 1, n (%)	128 (48)	58 (44)	70 (53)	0.11	69 (49)	59 (48)	0.97
Final post-PCI TIMI flow grade 3, n (%)	250 (95)	123 (92)	127 (97)	0.10	132 (93)	118 (97)	0.17
Total number of stents per culprit lesion	1.3±0.6	1.3±0.6	1.3±0.5	0.58	1.3±0.5	1.3±0.6	0.62
Mean stent diameter per culprit lesion (mm)	3.18±0.46	3.19±0.43	3.17±0.48	0.74	3.19±0.44	3.16±0.47	0.70
Total stent length per patients (mm)	26±13	27±14	26±13	0.46	26±13	27±14	0.92
Drug-eluting stent implantation, n (%)	68 (26)	34 (26)	34 (26)	0.94	35 (25)	33 (27)	0.66
Use of aspiration catheter, n (%)	163 (62)	75 (56)	88 (67)	0.07	80 (56)	83 (68)	0.05
Use of distal protection device, n (%)	50 (19)	24 (18)	26 (20)	0.71	25 (18)	25 (20)	0.55
Use of intravascular ultrasound, n (%)	210 (80)	105 (79)	105 (80)	0.81	109 (77)	101 (83)	0.22
Insertion of intra-aortic balloon pump, n (%)	49 (19)	31 (23)	18 (14)	<0.05	32 (23)	17 (14)	0.07
Femoral approach, n (%)	182 (69)	91 (68)	91 (69)	0.85	101 (71)	81 (66)	0.41

Values are expressed as n (%) or mean±standard deviation.
cIMT, carotid intima-media thickness; cPS, carotid plaque score; PCI, percutaneous coronary intervention; TIMI, Thrombosis In Myocardial Infarction.

measurements were averaged and expressed as the mean cIMT. The cPS was computed by summing the maximal thickness of the plaques in each segment on both sides (a+b+c+thickness of the contralateral plaques in each segment on both sides: **Fig. 1**) as described previously[27].

Clinical Follow-up and End Point

Clinical information was obtained from a review of the hospital record or by telephone contact with the patient, the family members, or the primary care physicians. Death was regarded as being of cardiac origin unless obvious non-cardiac causes could be identified. Stroke during follow-up was defined as ischemic or hemorrhagic stroke requiring hospitalization with symptoms lasting >24 h. Target vessel revascularization was defined as any repeat PCI or surgical bypass of any segment of the target vessel associated with symptoms or objective signs of ischemia. Stent thrombosis was assessed according to the definition of the Academic Research Consortium[28]. The primary endpoint of this study was major adverse cardiovascular events (MACEs), defined as a composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and target vessel revascularization.

Statistical Analysis

Comparisons between quantitative variables were performed with Student's *t*-test. Categorical variables were compared using the Chi-squared test. Multivariate analysis of independent predictors of adverse outcome was performed using the Cox proportional hazard regression model. Variables with $p<0.05$ on univariate analysis were selected for multivariate analysis in consideration of potential confounding variables. Continuous variables were dichotomized for the median in the multivariate model. We compared Kaplan–Meier estimates of endpoints using log-rank test. We performed receiver operating characteristic analysis and calculated the area under the receiver operator characteristic curve to estimate the predictive performance for MACEs. The area under the receiver operator characteristic curve was compared according to the method of Delong *et al.*[29]. Probability values of <0.05 were considered statistically significant. Statistical analyses were performed using JMP pro Version 12 (SAS institute, Cary, NC, USA).

Results

First, we dichotomized patients into two groups, according to the median values of the cPS and cIMT.

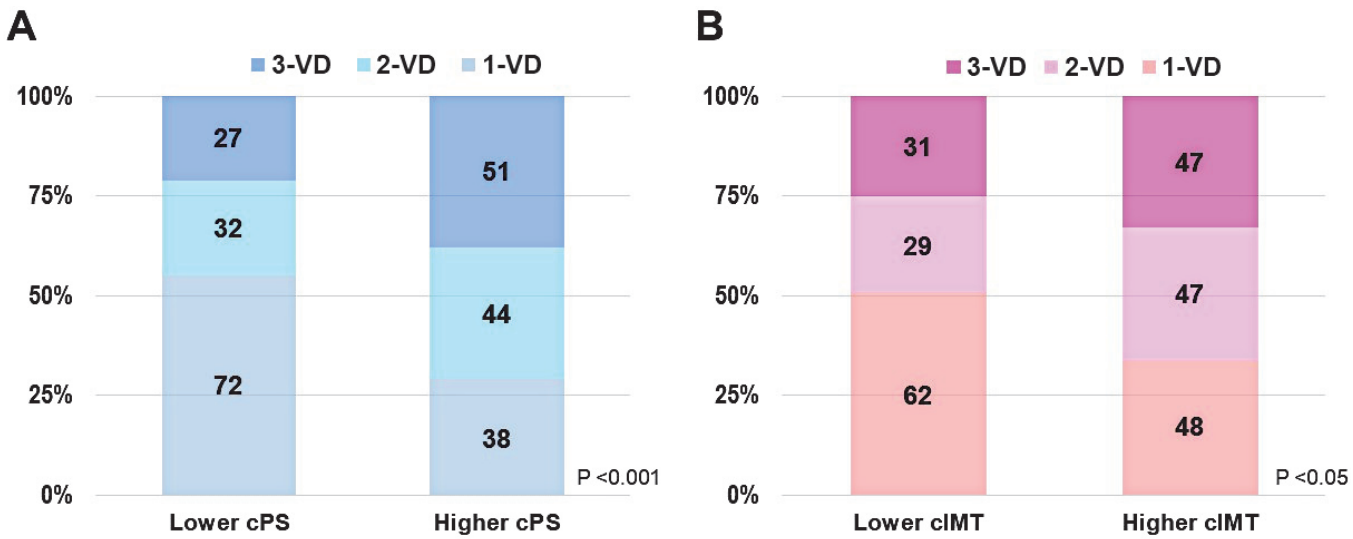

Fig. 2. Distribution of multivessel disease according to the severity of carotid atherosclerosis determined by carotid ultrasonography

Number of coronary arteries with significant lesions following coronary angiography according to the classification of the carotid artery atherosclerosis by the median of (A) cPS and (B) cIMT. The absolute number of patients in each category is indicated inside the bars. cIMT, carotid intima−media thickness; cPS, carotid plaque score; VD, vessel disease.

Table 3. Clinical outcome after PCI

	All (n=264)	cPS		P value	cIMT		P value
		Higher (≥9.8) (n=133)	Lower (<9.8) (n=131)		Higher (≥0.8 mm) (n=142)	Lower (<0.8 mm) (n=122)	
All-cause death	37 (14)	31 (23)	6 (5)	<0.001	30 (21)	7 (6)	<0.001
Cardiovascular death	24 (9)	20 (15)	4 (3)	<0.001	19 (13)	5 (4)	<0.05
Myocardial infarction	13 (5)	6 (5)	7 (5)	0.75	5 (4)	8 (7)	0.26
Definite stent thrombosis	6 (2)	4 (3)	2 (2)	0.42	3 (2)	3 (2)	0.85
Stroke	17 (6)	12 (9)	5 (4)	0.08	12 (8)	5 (4)	0.14
Target vessel revascularization	76 (29)	43 (32)	33 (25)	0.20	44 (31)	32 (26)	0.39
MACEs	121 (46)	77 (58)	44 (34)	<0.001	77 (54)	44 (36)	<0.05

Values are expressed as n (%).
cIMT, carotid intima-media thickness; cPS, carotid plaque score; MACEs, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.

The mean patient age was 68±11 years; 194 (73%) were male (Table 1). The angiographic and procedural characteristics are presented in Table 2. In coronary angiography, multivessel disease was observed in 154 patients (58%). As shown in Fig. 2, diseased coronary arteries increased significantly with increasing cPS and cIMT.

The median duration of follow-up for the survivors was 4.1 years (interquartile range: 2.1 to 6.4 years). Complete 1-, 2-, and 4-year follow-up information was obtained for 87%, 80%, and 59% of all patients, respectively. During follow-up, there were 121 incidents of MACEs. Outcomes of selected endpoints are shown in Table 3. We performed Cox proportional hazard regression analyses to identify predictors of MACEs (Table 4). On multivariate analysis (Table 4, model A), an ACEF score of ≥1.20 (hazard ratio [HR], 1.62; 95% confidence interval [CI], 1.11−2.39) and cPS of ≥9.8 (HR, 1.52; 95% CI, 1.01−2.31) were significantly related to MACEs. However, cIMT was no longer a significant factor for MACEs in multivariate analysis (HR, 1.27; 95% CI, 0.84−1.94). On the other hand, when the analysis was conducted by entering the variable of multivessel disease (Table 4, model B), the statistical significance of cPS was attenuated (HR, 1.22; 95% CI, 0.80−1.88). In the present study, we

Table 4. Univariate and multivariate predictors of MACEs

	Univariate		Multivariate (Model A)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (per 1 year increase)	1.02 (1.00−1.04)	<0.05*, **		
Male gender	1.21 (0.79−1.91)	0.39		
Diabetes mellitus	1.33 (0.92−1.91)	0.13		
CrCL (per 1 mL/min increase)	0.99 (0.98−0.99)	<0.001*, **		
Left ventricular EF (per 1% increase)	0.98 (0.97−0.99)	<0.05*, **		
ACEF score ≥1.20	1.86 (1.29−2.72)	<0.001	1.62 (1.11−2.39)	<0.05
cPS ≥9.8	1.81 (1.25−2.64)	<0.05**	1.52 (1.01−2.31)	<0.05
cIMT ≥0.8 mm	1.65 (1.14−2.41)	<0.05	1.27 (0.84−1.94)	0.25
Drug-eluting stent implantation	0.57 (0.34−0.90)	<0.05	0.58 (0.35−0.93)	<0.05
Insertion of intra-aortic balloon pump	1.65 (1.06−2.49)	<0.05	1.29 (0.82−1.97)	0.26
Multivessel disease	2.53 (1.69−3.88)	<0.001		
Clinical cPS ≥13.5	2.52 (1.72−3.76)	<0.001		

	Multivariate (Model B)		Multivariate (Model C)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (per 1 year increase)				
Male gender				
Diabetes mellitus				
CrCL (per 1 mL/min increase)				
Left ventricular EF (per 1% increase)				
ACEF score ≥1.20	1.50 (1.03−2.22)	<0.05		
cPS ≥9.8	1.22 (0.80−1.88)	0.36		
cIMT ≥0.8 mm	1.36 (0.90−2.07)	0.15	1.30 (0.89−1.93)	0.18
Drug-eluting stent implantation	0.53 (0.32−0.84)	<0.05	0.54 (0.32−0.85)	<0.05
Insertion of intra-aortic balloon pump	1.19 (0.76−1.81)	0.44	1.21 (0.77−1.84)	0.39
Multivessel disease	2.27 (1.49−3.56)	<0.001	2.14 (1.40−3.35)	<0.001
Clinical cPS ≥13.5			1.78 (1.18−2.75)	<0.05

ACEF, age, creatinine, and ejection fraction; CrCL, creatinine clearance; CI, confidence interval; cIMT, carotid intima-media thickness; cPS, carotid plaque score; EF, ejection fraction; HR, hazard ratio; MACEs, major adverse cardiovascular and cerebrovascular events; PCI, percutaneous coronary intervention.
Model A, adjusted for ACEF score, cPS, cIMT, drug-eluting stent implantation, and insertion of intra-aortic balloon pump.
Model B, adjusted for ACEF score, cPS, cIMT, drug-eluting stent implantation, and insertion of intra-aortic balloon pump, and multivessel disease.
Model C, adjusted for cIMT, drug-eluting stent implantation, insertion of intra-aortic balloon pump, multivessel disease, and clinical cPS.
*Age, CrCL, and left ventricular EF were not entered into the multivariate model A and B as these parameters were included in the ACEF score calculation.
**Age, CrCL, left ventricular EF, and cPS were not entered to the multivariate model C as these parameters were included in clinical cPS calculation.

developed a new combined risk scoring system (clinical cPS). The clinical cPS was calculated by multiplying the cPS by the modified ACEF score. Interestingly, clinical cPS was found to be significantly associated with MACEs, even after adjustment for multivessel disease (**Table 4**, model C: HR, 1.78; 95% CI, 1.18−2.75).

Freedom from MACEs at 5 years was 64% and 32% in the patients with lower and higher ACEF scores, respectively (**Fig. 3A**). Similarly, freedom from MACEs at 5 years was 61% and 39% in patients with lower and higher cPS, respectively (**Fig. 3B**). Furthermore, stratification of patients based on the median of the clinical cPS exhibited significantly different estimates for 5-year freedom from MACEs for the lower and higher risk groups: 71% and 31%, respectively (**Fig. 3C**). The area under the curve for the probability of MACEs for clinical cPS was much higher than that for the ACEF score and cPS alone (**Fig. 4**). The prognostic performances of the ACEF score, cPS, and clinical cPS compared with traditional risk factors are shown in **Supplementary Table 1**.

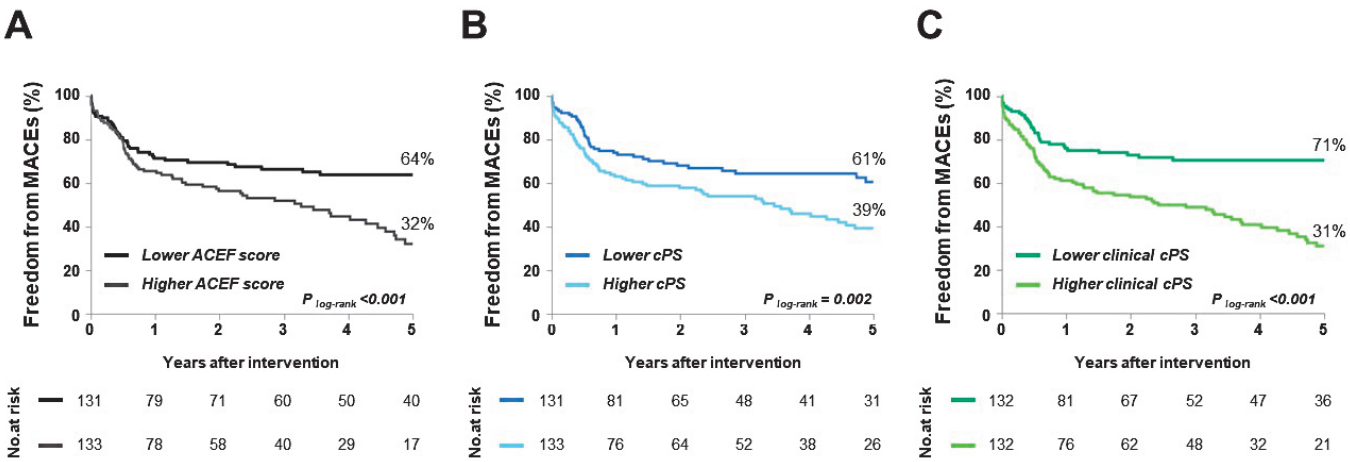

Fig. 3. Kaplan–Meier time-to-event curves for MACEs

Kaplan–Meier time-to-event curves were stratified across the median of (A) ACEF score, (B) cPS, and (C) clinical cPS for freedom from MACEs. The numbers of patients at risk at each time point are indicated below the graph. ACEF, age, creatinine, and ejection fraction; cPS, carotid plaque score; MACEs, major adverse cardiovascular and cerebrovascular events.

Discussion

This study provided the following important new findings: (1) both cPS and cIMT reflect the extents of coronary artery disease in patients with ACS; (2) cPS, but not cIMT, was a major predictor of MACEs in ACS; (3) the combination of cPS as an anatomical characteristic to the ACEF score, which is a simple clinical risk score, improved the prognostic ability in patients with ACS who underwent PCI. This is the first study to demonstrate the prognostic utility of cPS in patients with ACS. Furthermore, we demonstrated the importance of combining risk assessment by incorporating anatomical characteristics, as assessed by carotid ultrasonography, and the ACEF score, which is comprised of simple clinical characteristics.

Although several investigators have examined the predictive value of cIMT or other metrics obtained from carotid ultrasound in primary prevention[13, 14], the prognostic ability of cIMT in patients with established atherosclerotic vascular disease remains controversial[30-32]. The measurements obtained from carotid ultrasonography appear to be derived from similar components. However, progression of atheromatous plaques usually occurs at sites of low shear stress such as the bifurcation in the proximal internal carotid artery[33], which is of interest in calculating the cPS, thus contributing to the difference in performance in the detection of disease severity compared with cIMT. A recent study demonstrated a stronger association between cPS and the occurrence of cardiovascular events compared with cIMT in patients with hypertension[34].

Given the significant relationship between cPS and the incidence of cardiovascular outcomes, it is important to consider whether cPS offers incremental information beyond the known risk factors. Although the coexistence of peripheral artery disease has been reported as a more diffuse and complex atherosclerotic phenotype in patients undergoing PCI[35, 36], few data

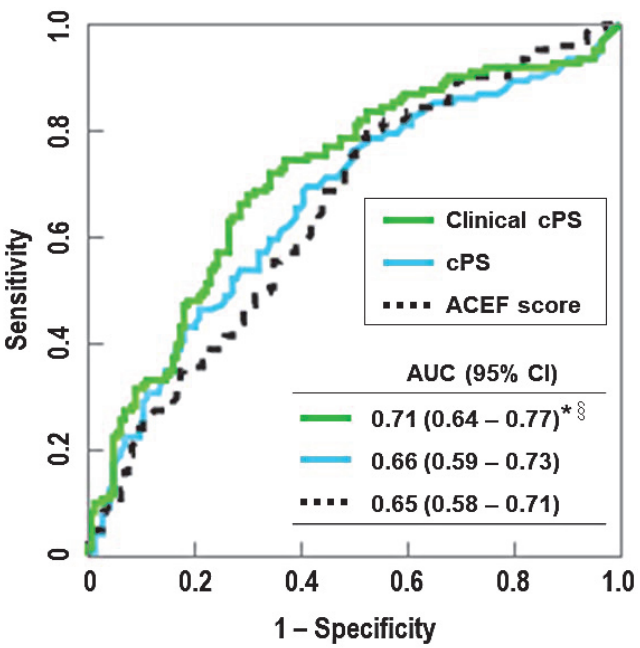

Fig. 4. Comparison of diagnostic performance for MACEs between ACEF score, cPS, and clinical cPS

*$p<0.05$ vs. ACEF score; §$p<0.05$ vs. cPS. ACEF, age, creatinine, and ejection fraction; AUC, area under the receiver operator characteristic curve; CI, confidence interval; cPS, carotid plaque score.

exist regarding potential improvement for risk stratification in evaluating subclinical carotid atherosclerosis over known risk factors in patients with coronary artery disease. In this respect, cPS is shown to be a promising factor as an anatomical characteristic that could refine risk assessment when combined with the clinical risk score. Although the incorporation of an angiographic scoring system was successful in improving the prognostic ability of the clinical risk score, the combined risk score requires both an invasive imaging modality and clinical characteristics; thus, risk assessment may only be performed after coronary angiography. Approaches of risk assessment by combining anatomical characteristics obtained using non-invasive imaging and a clinical risk score might extend to the patients considering coronary angiography. Furthermore, in the present study, an improvement in the ability of the clinical risk score to predict MACEs could be achieved by the combined risk score, although the clinical utility of the combined risk score appeared controversial for predicting a wide spectrum of adverse outcomes[37-39]. Thus, the assessment of subclinical carotid atherosclerosis using cPS may contribute to compensatory strategies for coronary angiographic risk scoring system in patients requiring coronary revascularization.

The present study has several limitations to consider. First, this was a retrospective study with a small sample size. In addition, although carotid ultrasonography was always performed to identify subclinical carotid atherosclerosis as part of our standard practice, many patients without carotid ultrasonography findings were excluded. Those patients who died as a result of ACS before carotid ultrasonography were not included in this study. Furthermore, our study consisted entirely of Japanese patients with ACS and, therefore, some caution should be taken when extending our findings to other cohorts. Despite these limitations, the present study could clearly show the importance of estimating subclinical carotid atherosclerosis with respect to predicting outcomes in ACS patients. Second, due to the very long enrolment period, significant differences in treatment strategies could exist over time. However, all patients in the present study underwent similar procedures such as coronary intervention. Third, statin intensity and combinations of antihypertensive drugs were different in this study population. Therefore, we could not take into account the association between the medical treatment and subsequent outcome. It is possible that regression of carotid atherosclerosis with drug administration reflects the prognostic benefit[40]. Finally, we did not assess the Framingham Risk Score, which is used as a reference risk model, when incorporating anatomical characteristics from a non-invasive imaging modality[41], because it remains unknown whether this risk assessment is applicable to patients after myocardial infarction.

Conclusion

This is the first study to demonstrate the prognostic utility of cPS in patients with ACS. Furthermore, the cPS is a promising factor as an anatomical characteristic that could refine risk assessment through incorporation into a simple clinical risk score. Approaches of risk assessment by combining anatomical characteristics obtained using non-invasive imaging and a clinical risk score warrant further investigation in a large prospective trial.

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Disclosures

None.

References

1) Arai H, Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M; JAPAN-ACS Investigators: More intensive lipid lowering is associated with regression of coronary atherosclerosis in diabetic patients with acute coronary syndrome--sub-analysis of JAPAN-ACS study. J Atheroscler Thromb, 2010; 17: 1096-1107
2) Teramoto R, Sakata K, Miwa K, Matsubara T, Yasuda T, Inoue M, Okada H, Kanaya H, Kawashiri MA, Yamagishi M, Hayashi K: Impact of Distal Protection with Filter-Type Device on Long-term Outcome after Percutaneous Coronary Intervention for Acute Myocardial Infarction: Clinical Results with Filtrap®. J Atheroscler Thromb, 2016; 23: 1313-1323
3) Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators: Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med, 2014; 371: 2155-2166
4) Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM: Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. Circulation, 1995; 91: 1659-1668
5) Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier

IG, Yandle TG: B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. Circulation, 2003; 107: 2786-2792
6) Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med, 2004; 351: 1285-1295
7) Wykrzykowska JJ, Garg S, Onuma Y, de Vries T, Goedhart D, Morel MA, van Es GA, Buszman P, Linke A, Ischinger T, Klauss V, Corti R, Eberli F, Wijns W, Morice MC, di Mario C, van Geuns RJ, Juni P, Windecker S, Serruys PW: Value of age, creatinine, and ejection fraction (ACEF score) in assessing risk in patients undergoing percutaneous coronary interventions in the 'All-Comers' LEADERS trial. Circ Cardiovasc Interv, 2011; 4: 47-56
8) Lee JH, Bae MH, Yang DH, Park HS, Cho Y, Jeong MH, Kim YJ, Kim KS, Hur SH, Seong IW, Cho MC, Kim CJ, Chae SC; Korea Acute Myocardial Infarction Registry Investigators: Prognostic value of the age, creatinine, and ejection fraction score for 1-year mortality in 30-day survivors who underwent percutaneous coronary intervention after acute myocardial infarction. Am J Cardiol, 2015; 115: 1167-1173
9) Liu YH, Liu Y, Zhou YL, He PC, Yu DQ, Li LW, Xie NJ, Guo W, Tan N, Chen JY: Comparison of Different Risk Scores for Predicting Contrast Induced Nephropathy and Outcomes After Primary Percutaneous Coronary Intervention in Patients With ST Elevation Myocardial Infarction. Am J Cardiol, 2016; 117: 1896-1903
10) Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K: Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. Eur Heart J, 2012; 33: 113-119
11) O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr: Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med, 1999; 340: 14-22
12) Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr: Carotid-wall intima-media thickness and cardiovascular events. N Engl J Med, 2011; 365: 213-221
13) Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, Volcik K, Boerwinkle E, Ballantyne CM: Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol, 2010; 55: 1600-1607
14) Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I: Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study. Stroke, 2011; 42: 972-978
15) Nezu T, Hosomi N, Aoki S, Matsumoto M: Carotid Intima-Media Thickness for Atherosclerosis. J Atheroscler Thromb, 2016; 23: 18-31
16) Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG; PRAMI Investigators: Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med, 2013; 369: 1115-1123
17) Claessen BE, van der Schaaf RJ, Verouden NJ, Stegenga NK, Engstrom AE, Sjauw KD, Kikkert WJ, Vis MM, Baan J Jr, Koch KT, de Winter RJ, Tijssen JG, Piek JJ, Henriques JP: Evaluation of the effect of a concurrent chronic total occlusion on long-term mortality and left ventricular function in patients after primary percutaneous coronary intervention. JACC Cardiovasc Interv, 2009; 2: 1128-1134
18) Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, Serruys PW; ARTS-II Investigators: A new tool for the risk stratification of patients with complex coronary artery disease: the Clinical SYNTAX Score. Circ Cardiovasc Interv, 2010; 3: 317-326
19) Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, Sanfilippo A, Capranzano P, Tamburino C: EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. Am Heart J, 2010; 159: 103-109
20) Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW: Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet, 2013; 381: 639-650
21) Nakahashi T, Sakata K, Nomura A, Yakuta Y, Gamou T, Terai H, Horita Y, Ikeda M, Namura M, Takamura M, Kawashiri MA, Yamagishi M, Hayashi K: Impact of Baseline Angiographic Complexities Determined by Coronary Artery Bypass Grafting SYNTAX Score on the Prediction of Outcome After Percutaneous Coronary Intervention. Am J Cardiol, 2016; 118: 974-979
22) Nayak AK, Kawamura A, Nesto RW, Davis G, Jarbeau J, Pyne CT, Gossman DE, Piemonte TC, Riskalla N, Chauhan MS: Myocardial infarction as a presentation of clinical in-stent restenosis. Circ J, 2006; 70: 1026-1029
23) Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E: The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. J Am Coll Cardiol, 1997; 30: 133-140
24) Tanimoto S, Ikari Y, Tanabe K, Yachi S, Nakajima H, Nakayama T, Hatori M, Nakazawa G, Onuma Y, Higashikuni Y, Yamamoto H, Tooda E, Hara K: Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population. Stroke, 2005; 36: 2094-2098
25) Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron, 1976; 16: 31-41
26) Terminology and Diagnostic Criteria Committee, Japan Society of Ultrasonics in Medicine: Standard method for ultrasound evaluation of carotid artery lesions. J Med Ultrason, 2009; 36: 219-226
27) Handa N, Matsumoto M, Maeda H, Hougaku H, Ogawa

S, Fukunaga R, Yoneda S, Kimura K, Kamada T: Ultrasonic evaluation of early carotid atherosclerosis. Stroke, 1990; 21: 1567-1572
28) Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium: Clinical end points in coronary stent trials: a case for standardized definitions. Circulation, 2007; 115: 2344-2351
29) DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics, 1988; 44: 837-845
30) Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP: The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med, 1998; 128: 262-269
31) del Sol AI, Moons KG, Hollander M, Hofman A, Koudstaal PJ, Grobbee DE, Breteler MM, Witteman JC, Bots ML: Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. Stroke, 2001; 32: 1532-1538
32) Keo HH, Baumgartner I, Hirsch AT, Duval S, Steg PG, Pasquet B, Bhatt DL, Roether J; REACH Registry Investigators: Carotid plaque and intima-media thickness and the incidence of ischemic events in patients with atherosclerotic vascular disease. Vasc Med, 2011; 16: 323-330
33) Solberg LA, Eggen DA: Localization and sequence of development of atherosclerotic lesions in the carotid and vertebral arteries. Circulation, 1971; 43: 711-724
34) Kawai T, Ohishi M, Takeya Y, Onishi M, Ito N, Oguro R, Yamamoto K, Kamide K, Rakugi H: Carotid plaque score and intima media thickness as predictors of stroke and mortality in hypertensive patients. Hypertens Res, 2013; 36: 902-909
35) Kim HL, Seo JB, Chung WY, Zo JH, Kim MA, Kim SH: Prognostic value of the ankle-brachial index in patients undergoing drug-eluting stent implantation. J Atheroscler Thromb, 2015; 22: 27-37
36) Miura T, Soga Y, Doijiri T, Aihara H, Yokoi H, Iwabuchi M, Nobuyoshi M: Prevalence and clinical outcome of polyvascular atherosclerotic disease in patients undergoing coronary intervention. Circ J, 2013; 77: 89-95
37) Jou YL, Lu TM, Chen YH, Sung SH, Wang KL, Huang SS, Lin WT, Chan WL, Lin SJ: Comparison of the predictive value of EuroSCORE, SYNTAX score, and clinical SYNTAX score for outcomes of patients undergoing percutaneous coronary intervention for unprotected left main coronary artery disease. Catheter Cardiovasc Interv, 2012; 80: 222-230
38) Kovacic JC, Limaye AM, Sartori S, Lee P, Patel R, Chandela S, Trost B, Roy S, Harari R, Narechania B, Karajgikar R, Kim MC, Krishnan P, Moreno P, Baber U, Mehran R, Dangas G, Kini AS, Sharma SK: Comparison of six risk scores in patients with triple vessel coronary artery disease undergoing PCI: competing factors influence mortality, myocardial infarction, and target lesion revascularization. Catheter Cardiovasc Interv, 2013; 82: 855-868
39) Park KW, Kang J, Kang SH, Ahn HS, Lee HY, Kang HJ, Koo BK, Chae IH, Youn TJ, Oh BH, Park YB, Kandzari DE, Kim HS: Usefulness of the SYNTAX and clinical SYNTAX scores in predicting clinical outcome after unrestricted use of sirolimus- and everolimus-eluting Stents. Circ J, 2013; 77: 2912-2921
40) Huang LC, Lin RT, Chen CF, Chen CH, Juo SH, Lin HF: Predictors of Carotid Intima-Media Thickness and Plaque Progression in a Chinese Population. J Atheroscler Thromb, 2016; 23: 940-949
41) Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC: Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA, 2004; 291: 210-215

Supplementary Table 1. Comparison of predictive models for MACEs

Risk model	Area under the curve (95% CI)	*P* value
Traditional risk factors	0.611 (0.541–0.676)	Reference
Traditional risk factors + ACEF score	0.660 (0.591–0.723)	< 0.05
Traditional risk factors + cPS	0.677 (0.609–0.738)	< 0.05
Traditional risk factors + clinical cPS	0.695 (0.628–0.754)	< 0.05

Traditional risk factors included age, hypertension, diabetes mellitus, dyslipidemia, and current smoker. ACEF, age, creatinine, and ejection fraction; CI, confidence interval; cPS, carotid plaque score; MACEs, major adverse cardiovascular and cerebrovascular events.