

# 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<sup>2</sup>. The endpoint of this study was major adverse cardiovascular and cerebrovascular events (MACEs), defined as all-cause death, myocardial infarction, stroke, 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<sup>1-3</sup>. Age, ejection fraction, and renal function have been identified as powerful predictors of ACS in patients after myocardial infarction<sup>4-6</sup>. 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<sup>7-9</sup>; however, this clinical risk model does not contain anatomical characteristics that reflect the severity of coronary artery disease and subsequent outcome.

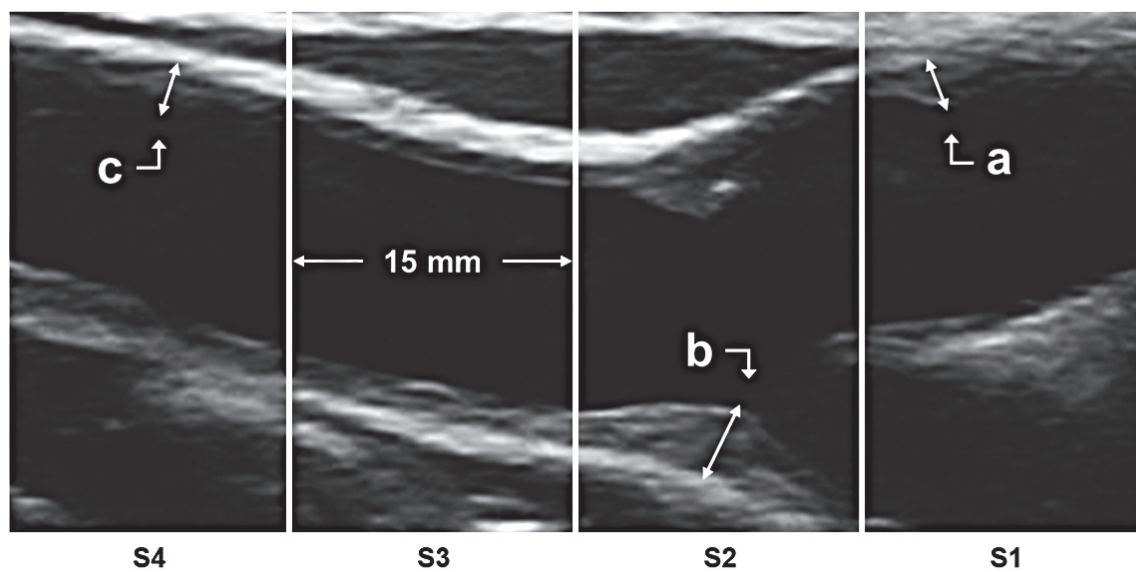
Non-invasive determination of carotid intima-media thickness (cIMT) using high-resolution B-mode ultrasonography has been reported in the diagnosis of subclinical carotid atherosclerosis as both a surrogate marker of coronary atherosclerosis and as a predictor

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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<sup>10-15</sup>). In addition to the robust association between coronary angiographic severity and prognosis in patients with ACS<sup>16,17</sup>), 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<sup>10</sup>). Since previous studies of angiographic risk score have demonstrated the importance of combining clinical and anatomical factors for risk stratification in patients undergoing PCI<sup>18-21</sup>), 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<sup>22</sup>). 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<sup>23</sup>).

**Table 1.** Baseline clinical characteristics

Variable	All (n=264)	cPS		P value	cIMT		P value
		Higher ( $\geq 9.8$ ) (n=133)	Lower ( $< 9.8$ ) (n=131)		Higher ( $\geq 0.8$ mm) (n=142)	Lower ( $< 0.8$ mm) (n=122)	
Age, years	68 $\pm$ 11	71 $\pm$ 9	64 $\pm$ 12	<0.001	71 $\pm$ 10	65 $\pm$ 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 $\pm$ 40	61 $\pm$ 34	82 $\pm$ 42	<0.001	68 $\pm$ 39	75 $\pm$ 41	0.20
Left ventricular EF (%)	58 $\pm$ 14	56 $\pm$ 14	59 $\pm$ 13	0.13	56 $\pm$ 14	59 $\pm$ 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
$\beta$ -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  $\pm$  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  $\geq 50\%$  in a major coronary artery<sup>24</sup>. 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  $\geq 50\%$  luminal narrowing in more than 2-vessels or in the left main trunk. Hypertension was defined as a blood pressure  $\geq 140/90$  mmHg or requiring treatment with antihypertensive medications. Diabetes mellitus was defined as HbA1c  $\geq 6.5\%$ , plasma glucose  $\geq 200$  mg/dL, or requiring treatment with insulin or hypoglycemic agents. Dyslipidemia was defined as a serum total cholesterol concentration  $\geq 220$  mg/dL, a low-density lipoprotein-cholesterol concentration  $\geq 140$  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<sup>7</sup>). 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<sup>2</sup> (up to a maximum of 6 points)<sup>18</sup>. Creatinine clearance was calculated using the Cockcroft-Gault equation<sup>25</sup>. 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<sup>26</sup>. 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<sup>27</sup>.

### Clinical Follow-up and End Point

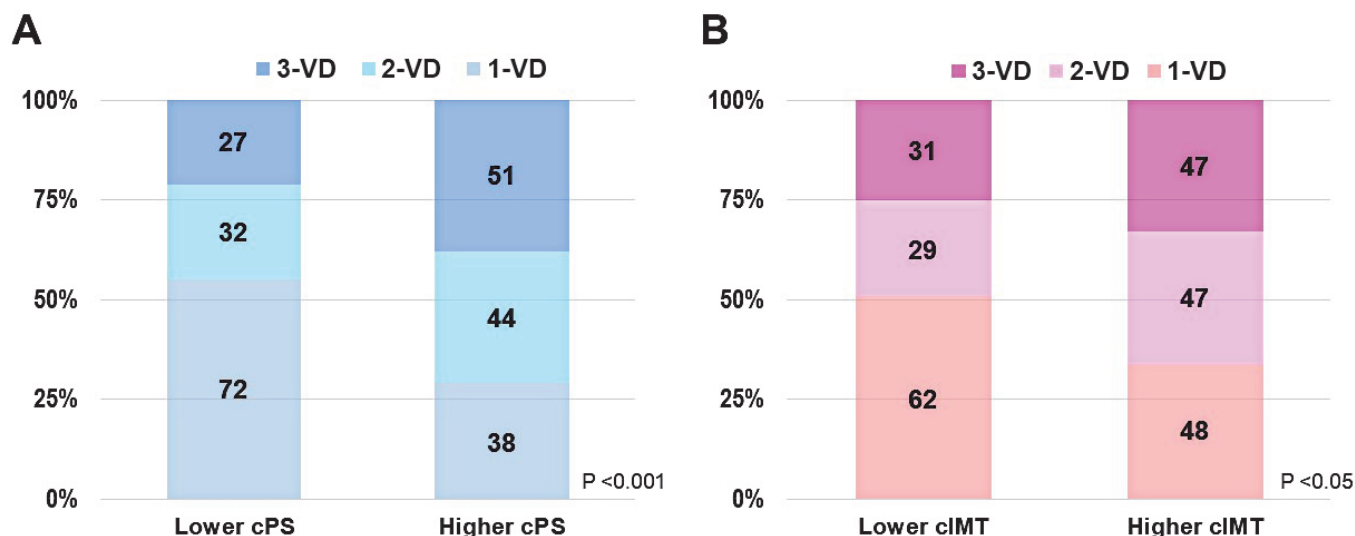
Clinical information was obtained from a review of the hospital record or by telephone contact with the patient, the family members, or the primary care physicians. Death was regarded as being of cardiac origin unless obvious non-cardiac causes could be identified. Stroke during follow-up was defined 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<sup>28</sup>. 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.*<sup>29</sup>. 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 ( $\geq 9.8$ ) (n = 133)	Lower ( $< 9.8$ ) (n = 131)		Higher ( $\geq 0.8$ 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  $68 \pm 11$  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  $\geq 1.20$  (hazard ratio [HR], 1.62; 95% confidence interval [CI], 1.11–2.39) and cPS of  $\geq 9.8$  (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 <sup>*,**</sup>		
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 <sup>*,**</sup>		
Left ventricular EF (per 1% increase)	0.98 (0.97–0.99)	< 0.05 <sup>*,**</sup>		
ACEF score $\geq$ 1.20	1.86 (1.29–2.72)	< 0.001	1.62 (1.11–2.39)	< 0.05
cPS $\geq$ 9.8	1.81 (1.25–2.64)	< 0.05 <sup>**</sup>	1.52 (1.01–2.31)	< 0.05
cIMT $\geq$ 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 $\geq$ 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 $\geq$ 1.20	1.50 (1.03–2.22)	< 0.05		
cPS $\geq$ 9.8	1.22 (0.80–1.88)	0.36		
cIMT $\geq$ 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 $\geq$ 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.

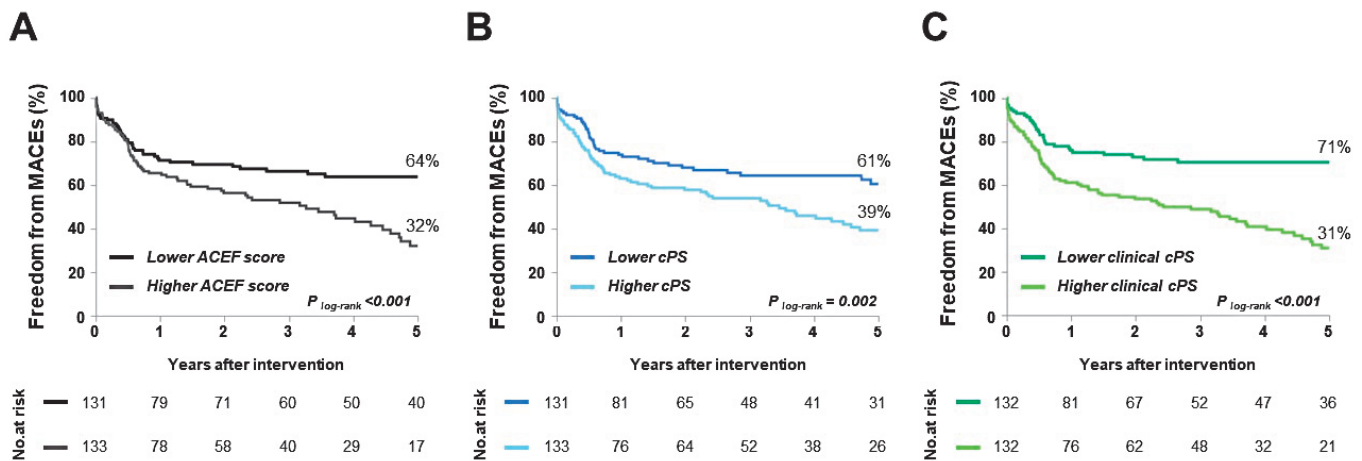
\*Age, CrCL, and left ventricular EF were not entered into the multivariate model A and B as these parameters were included in the ACEF score calculation.

\*\*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

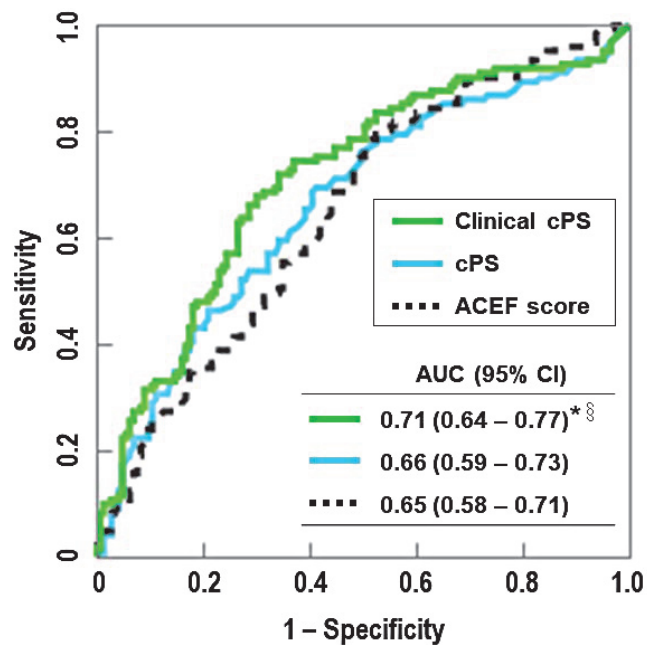
Kaplan–Meier time-to-event curves were stratified across the median of (A) ACEF score, (B) cPS, and (C) clinical cPS for freedom from MACEs. The numbers of patients at risk at each time point are indicated below the graph. ACEF, age, creatinine, and ejection fraction; cPS, carotid plaque score; MACEs, 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<sup>13, 14</sup>, the prognostic ability of cIMT in patients with established atherosclerotic vascular disease remains controversial<sup>30-32</sup>. 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<sup>33</sup>, 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<sup>34</sup>.

Given the significant relationship between cPS and



**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.

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<sup>35, 36</sup>, few data

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<sup>37-39</sup>). 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<sup>40</sup>). 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<sup>41</sup>), 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.

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**Supplementary Table 1.** Comparison of predictive models for MACEs

Risk model	Area under the curve (95% CI)	<i>P</i> 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.