S100A12 as a Marker to Predict Cardiovascular Events in Patients With Chronic Coronary Artery Disease

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Background: S100A12, a calgranulin family protein released from white blood cells, is involved in inflammatory cardiovascular disease. It was hypothesized that the plasma level of S100A12 can be used to predict outcome in patients with chronic coronary artery disease (CAD). The purpose of this study was to clarify the clinical significance of S100A12 in patients with stable CAD.

Methods and Results: A total of 652 patients with stable CAD were studied. All patients underwent percutaneous coronary intervention and successful revascularization. Major adverse cardiovascular events (MACE) were defined as a composite of events of CHF, recurrence of angina pectoris, acute myocardial infarction, stroke, critical arrhythmia, intervention to peripheral arteries and cardiac death. The mean follow-up period was 973 ± 639 days. MACE occurred in 108 patients (16.6%). Plasma S100A12 level had a significant positive correlation with high-sensitivity C-reactive protein (hs-CRP) level. On Kaplan-Meier curve analysis the incidence of MACE was significantly different among S100A12 quartiles ($P=0.026$). The highest S100A12 quartile (Q4) had a significantly higher MACE rate than the lowest quartile (Q1) ($P=0.002$). In contrast, hs-CRP was not significant for predicting MACE in the present subjects ($P=0.074$). A Cox proportional hazard model showed that S100A12 was an independent factor for predicting MACE in multivariate models.

Conclusions: S100A12 could be a novel biomarker for predicting cardiovascular events for predicting MACE in patients with stable CAD. (*Circ J* 2012; **76**: 2647–2652)

Key Words: Atherosclerosis; Inflammation; Leukocyte

Despite the recent development of a coronary revascularization method for patients with chronic coronary artery disease (CAD), critical cardiovascular events such as acute myocardial infarction and congestive heart failure (CHF) remain problematic. A drug-eluting stent has drastically reduced target lesion restenosis as indicated in the SIRIUS trial,^{1–4} but the prognosis of CAD patients did not improve sufficiently and the number of major adverse cardiovascular events (MACE) did not decrease even after the stent implantation.^{4,5} Therefore, the detection and management of high-risk patients is important.

S100A12 is a member of the S100 calcium-binding protein family secreted from white blood cells. To date, more than 20 members of this family have been identified. Each isoform of S100 has tissue-specific expression.⁶ S100A12 is expressed in granulocytes and activated monocytes/macrophages and is characterized by 2 calcium-binding EF-hands and consists of 9–14-kDa low-molecular acidic proteins.^{7–9} Interestingly, S100A12 binds to receptor for advanced glycation-end prod-

ucts (RAGE), leading to the upregulation of nuclear factor κ B (NF κ B) expression.⁶ Binding of S100A12 to RAGE induces secretion of cytokines via an NF κ B-mediated mechanism. Thus S100A12 is also termed extracellular newly identified RAGE-binding protein (EN-RAGE). In addition, S100A12 has remarkable chemotactic activity, comparable with other chemotactic agents.¹⁰ S100A12 is a mediator that increases inflammation and tumorigenesis,^{11–13} together with other cytokines.^{10,14}

S100A12 is reported to be involved in chronic inflammatory diseases such as rheumatoid arthritis,^{15,16} inflammatory bowel syndrome¹¹ and Kawasaki disease.¹⁷ We hypothesized that S100A12, a newly identified atherogenic molecule, is related to cardiovascular events in atherosclerotic coronary disease. In this study we measured plasma levels of S100A12 and investigated their clinical significance in patients with chronic CAD.

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Table 1. Baseline Subject Characteristics

Age (years), mean $\pm$ SD	64.1 $\pm$ 9.6
Male	533 (81.7)
BMI (kg/m ²)	24.2 $\pm$ 0.1
Hypertension	481 (73.8)
Dyslipidemia	427 (65.5)
DM	278 (42.6)
Current smoker	234 (35.9)
FH of CAD	139 (21.3)
hs-CRP (ng/ml)	2,877 $\pm$ 277
eGFR (ml $\cdot$ min ⁻¹ $\cdot$ 1.73 m ⁻²)	68.1 $\pm$ 0.87
LVEF (%)	60.7 $\pm$ 0.5
History of MI	206 (31.6)
No. stenotic major vessels	
0-vessel disease	1 (0.2)
1-vessel disease	260 (39.9)
2-vessel disease	243 (37.3)
3-vessel disease	109 (16.7)
Left main trunk	39 (6.0)

Data given as mean $\pm$ SEM or n (%).

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, family history; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Methods

Patients

Consecutive patients who underwent coronary angiography at Jichi Medical University Hospital between November 2002 and August 2010 were included in this study. We studied 652 patients with stable CAD who underwent successful percutaneous coronary intervention (PCI) at the hospital. PCI was performed by standard catheterization via a 5- or 6-Fr sheath inserted into the patient's femoral or radial arteries with local anesthesia. Aspirin and heparin were given before the PCI. Coronary stents were implanted into the stenotic lesions using a balloon-mounted stent delivery system. Directional atherectomy and rotational atherectomy were performed according to the operators' decision. After the PCI, all patients were followed up regularly every 4–8 weeks. MACE was defined as a composite of events of readmission for CHF, readmission due to the recurrence of angina pectoris, acute myocardial infarction, stroke, critical arrhythmia, intervention to peripheral arteries and cardiac death.

We excluded patients with acute coronary syndrome, acute inflammatory disease, acute renal failure, hematological disorder, collagen disease, malignancy and those taking immunosuppressive medicine. If successful coronary revascularization was not accomplished, we also excluded the patients. Hypertension, dyslipidemia and diabetes mellitus were diagnosed according to the criteria in the guidelines for each disease.^{18–20} Left ventricular ejection fraction (LVEF) was measured using echocardiography with modified Simpson's method.

The Ethics Committee of Jichi Medical University approved the study protocol. All patients enrolled in this study provided informed consent.

Measurement of Plasma Biomarkers

Peripheral blood was taken before cardiac catheterization. Anti-coagulated samples were then centrifuged immediately at 1,000 $\times$ g (4°C, 15 min) and stored at –80°C until the assay.

Figure 1. (A) Plasma S100A12 level was not normally distributed, therefore it was (B) logarithmically transformed. (A) Mean plasma S100A12 was 11.1 $\pm$ 26.6 ng/ml (SE, 1.04 ng/ml). The 95% confidence interval ranged from 9.05 to 13.14 ng/ml. Maximum and minimum values were 0.039 and 498.4 ng/ml, respectively. Median S100A12 level was 6.50 ng/ml. Log-S100A12, logarithmically transformed plasma S100A12.

The plasma concentration of S100A12 was determined using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (Cyclex, Nagano, Japan). The lower limit of S100A12 detection was 78 pg/ml. The intra- and inter-assay variation of the kit was 3.0% and 6.6%, respectively. The kit does not detect other S100 proteins such as S100A8 and 9. The sampling time and feeding did not influence the measurement of S100A12.

High-sensitivity C-reactive protein (hs-CRP) was measured using the latex nephelometry method described by Ledue et al.²¹

Statistical Analysis

All data are expressed as mean $\pm$ SEM unless otherwise indicated. The significance of differences between 4 groups was

determined using Jonckheere-Terpstra test. Categorical variables were expressed as percentages and analyzed using chi-square test. Correlations were analyzed using Spearman's correlation coefficient. Multiple regression, Kaplan-Meier survival curve and Cox proportional hazard model analyses were conducted using SPSS version 16.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Baseline Subject Characteristics

A total of 652 patients (age 29–85 years) were studied. The baseline subject characteristics are listed in **Table 1**. In the case of cardiac catheterization, 997 lesions were treated (1.53 lesions/patient). Two hundred and eighty-six (28.8%) were in the right coronary artery, 436 (43.7%) in the left anterior descending artery, 228 (22.9%) in the left circumflex artery, 33 (3.3%) in the left main trunk and 14 (1.4%) in the vein graft lesions. Nine hundred and forty-five lesions were treated with coronary stents, including 712 drug-eluting stents and 233 bare metal stents. One lesion was treated with a cutting balloon, 30 lesions by plain old balloon angioplasty, 4 lesions by directional coronary atherectomy and 17 lesions with rotational atherectomy.

Plasma S100A12 Level and Clinical Parameters

The distribution of plasma S100A12 is given in **Figure 1**. Mean plasma S100A12 was 11.1 ng/ml with SD of 26.6 ng/ml and SE, 1.04 ng/ml. The 95% confidence interval ranged from 9.05 to 13.14 ng/ml. Maximum and minimum values were 0.039 and 498.4 ng/ml, respectively. The median S100A12 was 6.50 ng/ml. As shown in **Figure 1A**, S100A12 level did not have a normal distribution, therefore it was logarithmically transformed (**Figure 1B**).

First, we examined the simple correlation between plasma S100A12 level and clinical parameters. Similar to S100A12,

Table 2. Plasma S100A12 and Clinical Parameters

Clinical parameters	Correlation coefficient	P value
Age (years)	+0.071	0.072
BMI (kg/m ²)	−0.022	0.570
WBC count (μl)	+0.148	<0.001
RBC count (×10 ⁴ /μl)	−0.095	0.015
Platelet count (×10 ⁴ /μl)	+0.084	0.033
HbA _{1c} (%)	+0.058	0.145
AST (IU/L)	+0.066	0.092
ALT (IU/L)	−0.013	0.745
TC (mg/dl)	+0.020	0.618
Triglyceride (mg/dl)	+0.011	0.786
LDL-C (mg/dl)	+0.027	0.506
HDL-C (mg/dl)	+0.024	0.546
hs-CRP (ng/ml, log)	+0.248	0.001
eGFR (ml · min ^{−1} · 1.73 m ^{−2})	−0.027	0.488
LVEF (%)	−0.069	0.080

Triglyceride, hs-CRP and S100A12 data were logarithmically transformed due to non-parametric distribution.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RBC, red blood cell; TC, total cholesterol; WBC, white blood cell. Other abbreviations as in Table 1.

we used logarithmically transformed triglyceride and hs-CRP in the data analysis, because they did not follow a Gaussian distribution. **Table 2** lists the correlation between plasma S100A12 level and clinical parameters. The white blood cell count, the platelet count and hs-CRP had a significant positive correlation with plasma S100A12. The red blood cell count and plasma S100A12 level had a significant negative correlation. We then conducted multivariate linear regression analysis

Table 3. Baseline Subject Characteristics vs. S100A12 Quartile

S100A12 quartile	Q1	Q2	Q3	Q4
Age (years), mean ± SD	63.3±9.8	63.6±9.4	65.5±8.9	63.9±10.1
Gender (M/F)	129/34	141/22	125/38	138/25
BMI (kg/m ²)	24.3±0.3	24.3±0.2	23.8±0.2	24.3±0.3
Hypertension	115 (71)	126 (77)	126 (83)	120 (74)
Dyslipidemia	112 (69)	105 (64)	98 (60)	112 (69)
DM	59 (36)	70 (43)	71 (44)	78 (48)
Smoking	108 (66)	122 (75)	108 (66)	125 (77)
FH of CAD	32 (20)	39 (24)	31 (19)	37 (23)
WBC (μl)	6,223±1,202	6,644±1,375	6,465±122	7,022±142†
RBC (×10 ⁴ /μl)	435±5	431±5	423±5	429±47
Platelet (×10 ⁴ /μl)	21.4±0.5	23.7±0.5	22.2±0.5	24.5±0.8§
HbA _{1c} (%)	5.97±0.10	6.21±0.11	6.05±0.08	6.22±0.10
TC (mg/dl)	189±2.8	189±3.0	189±3.0	193±3.4
Triglyceride (mg/dl)	148±7.0	154±6.8	146±6.1	169±8.4
LDL-C (mg/dl)	110±2.6	109±2.7	112±2.6	110±1.3
HDL-C (mg/dl)	48±1.1	47±1.0	48±1.1	48±1.1
hs-CRP (ng/ml)	1,314±248	2,036±475	3,422±720	4,735±618†
eGFR (ml · min ^{−1} · 1.73 m ^{−2})	67.5±1.6	69.3±1.5	69.4±1.8	66.2±2.0
LVEF (%)	62.0±0.98	61.7±0.95	60.0±1.05	59.1±1.14*
S100A12 (ng/ml)	1.89±0.07	4.98±0.07	8.64±0.12	28.9±3.84†

Data given as mean ± SEM or n (%). * $P < 0.05$; § $P < 0.01$; † $P < 0.001$. Abbreviations as in Tables 1,2.

using a stepwise method (forward entry model). We set plasma S100A12 level as a responsive variable and the white blood cell count, red blood cell count, platelet count and hs-CRP as explanatory variables. We found that hs-CRP was significantly associated with plasma S100A12 level ($\beta=+0.246, P<0.001$).

S100A12 Level as a Predictor of MACE in Chronic CAD Patients

Next, we examined whether plasma S100A12 can be used to predict MACE after successful PCI. The mean follow-up period was 973 ± 639 days (25–2,190 days). MACE occurred in 108 patients (16.6%). Recurrence of angina pectoris occurred in 48 patients. Of these, 26 patients had restenosis of target vessels and 22 patients had new stenotic lesions. Two patients

were treated medically, 9 patients by balloon angioplasty, 36 by coronary stent implantation and 1 patient by coronary bypass surgery. Arrhythmic events occurred in 2 patients. One patient had atrial fibrillation with complete atrioventricular block and was treated with permanent pacemaker implantation. One patient was re-admitted due to ventricular tachycardia and was treated with oral amiodarone.

We divided the patients into 4 groups based on the percentile of plasma S100A12 level ($n=163$, respectively). The quartiles were: $0.039<3.384$ ng/ml (Q1, first quartile), $3.384<6.503$ ng/ml (Q2, second quartile), $6.503<11.414$ ng/ml (Q3, third quartile), and $11.414\text{--}498.4$ ng/ml (Q4, fourth quartile). The mean S100A12 in Q1, Q2, Q3 and Q4 was 1.89 ± 0.07 ng/ml, 4.98 ± 0.07 ng/ml, 8.64 ± 0.12 ng/ml, and 28.9 ± 3.84 ng/ml, re-

Table 4. Cardiovascular Events vs. S100A12 Quartile

S100A12 quartile	Q1	Q2	Q3	Q4
Congestive heart failure	4	7	6	12
Readmission due to angina pectoris	11	13	14	10
Acute myocardial infarction	1	5	1	5
Stroke	0	0	3	2
Critical arrhythmia	1	0	1	0
Intervention to peripheral arteries	4	0	1	2
Cardiac death	0	2	2	1
MACE	21	27	28	32

MACE, major adverse cardiovascular event (defined as composite events of readmission for congestive heart failure, readmission due to recurrence of angina pectoris, acute myocardial infarction, stroke, critical arrhythmia, intervention to peripheral arteries and cardiac death).

spectively. **Table 3** lists the subject baseline clinical characteristics according to quartile. White blood cell count, platelet count, hs-CRP and LVEF were significantly different among the 4 groups. As shown in **Figure 2A**, MACE rate was statistically significant among 4 groups according to Kaplan-Meier curve (log-rank test, $\chi^2=9.28$, $P=0.026$). On post-hoc analysis the difference in the MACE rate between Q1 and Q4 was significant ($P=0.002$). Because there was a significant correlation between S100A12 and hs-CRP, we also examined whether hs-CRP could predict MACE. We divided patients into 4 groups according to the percentile of hs-CRP (median, 762 ng/ml; Q1, 50–<304.5 ng/ml; Q2, 304.5–<762 ng/ml; Q3, 762–<1,900 ng/ml; Q4, 1,900–88,200 ng/ml). As shown in **Figure 2B**, on Kaplan-Meier curve analysis the difference of the MACE rate in hs-CRP quartiles was not significant (log rank test, $\chi^2=6.92$, $P=0.074$). We summarized the cardiovascular events in 4 groups (**Table 4**).

We analyzed the independent factors associated with MACE. We performed multivariate Cox proportional hazard model analysis with the stepwise method (forward entry). In model 1, we used demographic data (age, sex), classical coronary risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking, family history of CAD, and body mass index) and S100A12 level as explanatory variables. We found that hypertension, diabetes mellitus and S100A12 were independent factors for predicting MACE (**Table 5**). In model 2, we added established factors for predicting MACE (estimated glomerular filtration rate [eGFR], hs-CRP, LVEF, history of myocardial infarction, number of major stenotic vessels, and intervention without drug-eluting stents; using plain balloon angioplasty alone, atherectomy alone and bare metal stents) to model 1 as explanatory variables. As shown in **Table 3**, hypertension, eGFR, LVEF and S100A12 level were significant factors for predicting MACE. In model 3, we used systolic blood pressure, triglyceride, low-density lipoprotein, high-density lipoprotein, hemoglobin A_{1c} (HbA_{1c}), and Brinkman index instead of hypertension, dyslipidemia, diabetes mellitus, and smoking as explanatory variables in model 2, respectively. In this model, we found that systolic blood pressure, HbA_{1c}, eGFR, LVEF and S100A12 level were significant factors for predicting MACE.

We further analyzed the significance of S100A12 for each cardiovascular event in the S100A12 quartiles. Kaplan-Meier curve analysis showed that plasma S100A12 level was significantly associated with CHF ($P=0.043$) and stroke ($P=0.044$). Cox analysis (model 3) showed that S100A12 was a significant independent predictor for CHF (hazard ratio, 2.44; 95% confidence interval: 1.03–5.79, $P=0.043$) together with HbA_{1c}, eGFR,

Table 5. Independent Factors for Predicting MACE in CAD Patients

	HR (95% CI)	P value
Model 1		
Hypertension	2.66 (1.49–4.75)	0.001
Diabetes mellitus	1.52 (1.04–2.22)	0.031
S100A12 (ng/ml)	1.80 (1.17–2.76)	0.007
Model 2		
Hypertension	2.56 (1.43–4.59)	0.002
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	0.99 (0.98–1.00)	0.004
LVEF (%)	0.97 (0.96–0.98)	<0.001
S100A12 (ng/ml)	1.59 (1.05–2.42)	0.030
Model 3		
Systolic blood pressure	1.01 (1.00–1.02)	0.004
HbA _{1c} (%)	1.19 (1.05–1.35)	0.009
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)	0.99 (0.98–1.00)	0.005
LVEF (%)	0.97 (0.96–0.99)	<0.001
S100A12 (ng/ml)	1.64 (1.06–2.53)	0.025

S100A12 data were logarithmically transformed due to non-parametric distribution.

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,4.

and LVEF. The incidence of stroke was too small to perform Cox analysis. We found a weak association between plasma S100A12 level and acute myocardial infarction, although on log-rank test it was not statistically significant ($P=0.059$).

Discussion

The present study has shown that plasma S100A12 level is associated with hs-CRP level, suggesting that S100A12 reflects inflammation in patients with stable CAD. Inflammation might account for the relationship between S100A12 and blood cell count. Interestingly, plasma S100A12 level was consistently associated with cardiovascular events in our models. In contrast, we did not find a significant association between hs-CRP and MACE in the present subjects.

S100A12 is abundantly expressed in white blood cells.^{9,22,23} Foell et al reported that infliximab, an anti-tumor necrosis factor- α antibody, rapidly reduced S100A12 level, suggesting positive feedback mechanisms for S100A12 and other inflammatory cytokines.¹¹ In addition, the ligation of S100A12 to RAGE activates NF κ B, leading to numerous inflammatory steps. Interestingly, expression of soluble RAGE has been reported to be elevated in patients with acute myocardial infarction.²⁴ The S100A8/9 heterodimer, another S100A protein, has been associated with an increased risk of cardiovascular events in a case-control study using patients enrolled in the PROVEIT-TIMI22 trial.²⁵

In the present study, S100A12 was a significant predictor of MACE in patients with stable CAD. In particular, S100A12 was a predictor for the occurrence of CHF. We still do not know the precise role of S100A12 in CHF. We speculate that S100A12 is associated with impairment of the cardiac microcirculation and endothelial dysfunction in patients with CAD. Although S100A12 seemed to be related to the stroke, the number of events was too small to obtain confident results.

In contrast to S100A12, hs-CRP was not significant for predicting MACE in the present subjects. S100A12 showed a concentration-dependent increase in the MACE rate, whereas hs-CRP did not show such a relationship. It is possible that

inflammation not related to cardiovascular systems might have contributed to the elevation of hs-CRP. Previous studies have demonstrated that hs-CRP is a useful biomarker to predict MACE in various cardiovascular diseases.^{26,27} A larger number of subjects might show hs-CRP as a prognostic marker using the present study design. S100A12 might be a specific marker of the pathological process in the cardiovascular system. Similar to S100A, previous reports have shown the clinical significance of pentraxin 3 in cardiovascular disease.^{28–30} Furthermore, procalcitonin, a bacterial infection marker, has been reported to be a marker to predict cardiovascular events.³¹ These novel and specific biomarkers are needed for the risk stratification of patients with cardiovascular disease.

In conclusion, plasma S100A12 level could be a novel biomarker for predicting MACE in patients with stable CAD. Further study using a larger number of subjects is needed to clarify the precise role of S100A12 in cardiovascular disease.

Study Limitations

First, we measured the level of S100A12 before PCI. It might be useful to follow the changes in plasma S100A12 level after PCI to provide more information about the relationship between S100A12 and MACE in chronic CAD patients.

Second, plasma S100A12 level was below the detection limit in 4 patients. We calculated S100A12 concentration using the standard regression curve of ELISA in these subjects. Their measurements were 39 pg/ml, 39 pg/ml, 47 pg/ml and 68 pg/ml, respectively. These data might be inaccurate because they are under the detection limit.

Finally, the number of events such as acute myocardial infarction, re-vascularization of peripheral arteries and cardiac death was small. Further study is needed with a larger number of subjects to confirm the significance of S100A12 in these events.

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