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Complete List of Authors:	Abe, Naoyuki; Shinshu university, Kashima, Yuichiro; Shinshu university, Izawa, Atsushi Motoki, Hirohiko; Shinshu university, Ebisawa, Souichirou; Shinshu university school of medicine, cardiovascular medicine Miyashita, Yusuke; Shinshu University Graduate School of Medicine, Cardiovascular medicine Imamura, Hiroshi; Shinshu university, Ikeda, Uichi; Shinshu university, ; Shinshu University School of Medicine, Cardiovascular Medicine
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A two-year follow-up of oxidative stress levels in patients with ST-segment-elevation myocardial infarction: A subanalysis of the ALPS-AMI study

Naoyuki Abe[1], MD; Yuichiro Kashima[1], MD; Atsushi Izawa[1], MD; Hirohiko Motoki[1], MD; Souichiro Ebisawa[1], MD; Yusuke Miyashita[1], MD; Hiroshi Imamura[2], MD; Uichi Ikeda[1], MD

[1]Department of Cardiovascular Medicine and

[2]Department of Emergency and Intensive Care Medicine,

Shinshu University School of Medicine, Nagano, Japan

Correspondence: Yuichiro Kashima, MD

Department of Cardiovascular Medicine

Shinshu University School of Medicine

3-1-1 Asahi, Matsumoto, Nagano 390-0802, Japan

Phone: 81-263-37-3486

Fax: 81-263-37-3489

E-mail: ykashima@shinshu-u.ac.jp

Abstract

We sought to determine whether serial measurements of oxidative stress levels could serve as a predictive marker for cardiovascular (CV) events in patients with ST-segment-elevation myocardial infarction (STEMI). Biological antioxidant potential (BAP) levels were measured at admission and at 6, 12, and 24 months in 69 STEMI patients. The CV events abruptly increased 6-10 months after successful percutaneous coronary intervention in patients with STEMI and the 6-month BAP levels were significantly lower in patients with CV events (2456 [interquartile range: 2237-2615] μmol/L) than in those without (2849 [2575-2987] μmol/L, $P < 0.001$). A decreased 6-month BAP level was an independent and significant predictor of long-term CV events (hazard ratio = 2.45; 95% confidence intervals 1.10-5.78; $P = 0.04$). Our findings suggest that serial changes in antioxidant capacity, assessed by BAP levels, may serve as a predictive marker for CV events after STEMI.

Key-words: ST-segment-elevation myocardial infarction, oxidative stress, biological antioxidant potential, diacron-reactive oxygen metabolite

Introduction

Timely reperfusion by percutaneous coronary intervention (PCI) is the best therapeutic strategy for ST-segment-elevation myocardial infarction (STEMI) and its widespread use has significantly reduced mortality.[1,2] However, STEMI survivors are at a high risk of recurrent cardiovascular (CV) events such as sudden death, arrhythmia and congestive heart failure.

An imbalance between reactive oxygen species generation and antioxidant reserve (i.e. oxidative stress) is involved in the pathogenesis of CV disease.[3-5] Oxidative stress alters the structure and function of membrane phospholipids, proteins, and mitochondrial DNA, which support myocardial remodeling and cardiac functional failure in the ischemic-injured heart.[6] Oxidative stress also contributes to the apoptosis, proliferation, and migration of vascular smooth muscle cells and adventitial myofibroblast after stent deployment, resulting in restenosis.[7,8] In addition, PCI, including balloon angioplasty and bare-metal stent deployment, also induces pathophysiological levels of vascular oxidative stress, leading to post-procedural pathological changes such as restenosis,[9,10] stent thrombosis[8] and endothelial dysfunction.[11-13] However, it remains unclear whether serial measurements of oxidative stress levels could serve as predictive markers for CV events in STEMI patients after successful PCI. Therefore, we investigated oxidative stress levels for 2 years in STEMI patients who underwent PCI.

Material and methods

Study population

The present study constituted a subanalysis of the assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction (ALPS-AMI) study. The ALPS-AMI study was a prospective, randomized, open-label, multicenter study of 500 patients with acute myocardial infarction (AMI). The purpose of the ALPS-AMI study is a head-to-head comparison of the

effectiveness of clinical doses of lipophilic atorvastatin and hydrophilic pravastatin in Japan for secondary prevention after AMI. The study protocol has been previously reported.[14] Briefly, patients with AMI, who satisfied the inclusion criteria were enrolled and randomly allocated to receive either 10 mg/day of atorvastatin or pravastatin for 2 years, within 96 h of successful PCI. The treatment goal was the lowering of low-density lipoprotein-cholesterol (LDL-C) levels below 100 mg/dL. Statin doses were increased to 20 mg/day if the target LDL-C levels had not been achieved at 1 month.

In the present study, a subgroup of 69 STEMI patients from the ALPS-AMI study who were admitted to the Shinshu University hospital between June 2008 and December 2010 were enrolled and randomly divided into atorvastatin (n = 36) or pravastatin (n = 33) groups. Written consent was obtained from the patients before enrollment, and the Ethics Committee at Shinshu University School of Medicine approved the protocol. This study was performed in accordance with the Declaration of Helsinki.

Blood sampling and oxidative stress analysis

Peripheral blood was drawn from the left antecubital vein via a 20-gauge peripheral venous catheter (Surflo®, Terumo Medical Products, Somerset, NJ, USA) immediately before the primary PCI. Plasma was isolated from all samples within 1 h of collection and assayed immediately for diacron-reactive oxygen metabolite (dROM) and biological antioxidant potential (BAP) levels.

The plasma levels of dROM and BAP were used as markers of oxidative stress. The dROM and BAP levels represent the total amount of peroxidized metabolites and serum antioxidant capacity, respectively.[15,16] The dROM and BAP levels were determined by a Free Radical Elective Evaluator (Diacron International, Grosseto, Italy) using commercial assay kits

(Diacron SRL, Grosseto, Italy). dROM levels were expressed in Carratelli units (U Carr), with 1 U Carr corresponding to 0.8 mg/L H_2O_2. The normal range of dROM is 250-300 U Carr. The BAP measurement is based on the ability of a colored solution, containing a source of ferric (Fe^{3+}) ions bound to a chromogenic substrate (thiocyanate derivative), to decolor when Fe^{3+} ions are reduced to ferrous ions (Fe^{2+}) by the reducing activity of blood samples. This chromatic change was read using a photometer at 505 nm. Preliminary data from nonuremic healthy individuals indicated that the normal BAP level is >2200 μmol/L.

Follow-up

All study subjects were followed as outpatients and underwent physical examination at least twice a month. The peripheral dROM and BAP levels were measured immediately before primary PCI and at 6, 12 and 24 months. All blood samples, except for baseline samples, were obtained in the morning following overnight fasting, to exclude the effects of diurnal and dietary variations in oxidative stress levels.

Endpoints

The endpoints of the present study were the same as the primary endpoints of the ALPS-AMI study: death due to any cause, nonfatal MI, nonfatal stroke, unstable angina, or congestive heart failure requiring hospital admission, and any type of coronary revascularization occurring at least 28 days after admission. The endpoints were strictly evaluated by the Endpoints Classification Committee of the ALPS-AMI study. While classifying the endpoint of the patients, the principal investigators were not informed about the group to which the patient belonged.

Statistical analysis

Statistical analysis was performed using SPSS Ver.18.0 (SPSS, Chicago, IL, USA). Unless otherwise stated, data are presented as mean ± standard deviation, if normally distributed, and as median with interquartile range (25^{th}-75^{th} percentiles), if non-normally distributed. An unpaired 2-tailed Student's *t*-test was used for normally distributed intergroup comparisons. Non-normally distributed, unpaired data were analyzed using a Mann-Whitney test. Paired non-normally distributed data were analyzed with a Wilcoxon signed-rank test. Categorical variables were compared using the chi-square (χ^2) test. For comparisons between multiple groups, we determined the significance of intergroup differences by one-way analysis of variance (ANOVA), followed by the Steel-Dwass multiple comparison procedure. The endpoints were analyzed, considering the timing of the first event, using Cox proportional hazards models to evaluate the clinical prognostic value of decreased BAP levels. Hazard ratios (HR) and 95% confidence intervals (CI) were also determined. A receiver operating characteristic (ROC) curve of the decreased BAP levels was created to assess the diagnostic performance of these levels for predicting CV events. Cumulative event curves were plotted by the Kaplan-Meier method and the difference was assessed by a log-rank test. A $p < 0.05$ was considered significant.

Results

Table 1 summarizes the characteristics of the patients with (n = 26) and without (n = 43) a CV event. The characteristics of the patients within the atorvastatin (n = 36) and pravastatin groups (n = 33) at baseline and 24 months are shown in Table 2 and 3, respectively. At baseline, no intergroup differences were noted in age, sex, body mass index, renal function, medications, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, hemoglobin

A_{1c}, brain natriuretic peptide levels, or diameter and length of stents between the patients with and without CV events, or the atorvastatin and pravastatin groups. During the follow-up period, there were 26 CV events, including 4 CV deaths, 17 PCIs due to restenosis after bare-metal stent deployment, 3 coronary artery bypass grafting surgeries, and 2 congestive heart failures requiring hospital admission.

In the entire patient population, the 6- and 12-month dROM levels were significantly decreased compared with those at baseline, but no differences were found between the baseline and 24-month dROM levels (Figure 1A). The BAP levels gradually increased and the 12- and 24-month BAP levels were significantly higher than those at baseline (Figure 1B).

When the oxidative stress levels between patients with or without CV events were compared, no intergroup differences in the dROM levels were found during the study period (Figure 2A). However, the 6-month BAP levels were significantly lower in patients with CV events (2456 [interquartile range: 2237-2615] μmol/L) than in those without (2849 [2575-2987] μmol/L, $P < 0.001$; Figure 2B).

The area under the ROC curve for the ability of the 6-month BAP levels to predict the primary endpoints was 0.659 (95% CI, 0.528-0.791, $P = 0.035$; sensitivity, 0.500; specificity, 0.759; Figure 3A), and the optimal cut-off 6-month BAP level was 2718 μmol/L. In patients with STEMI, the events abruptly increased from 6 to 10 months after successful primary PCI, and few events were observed from 12 to 24 months (Figure 3B). The temporal decreases in BAP levels occurred concomitantly with the occurrence of CV events. Kaplan-Meier analysis for all of the primary endpoints showed that patients with decreased 6 month BAP levels (BAP levels ≤2718 μmol/L) had a significantly lower event-free rate than did those without ($P = 0.024$; Figure 3B). Furthermore, a 6-month BAP level ≤2718 μmol/L was found to be an independent predictor of the primary endpoints (HR, 2.45; 95% CI, 1.10-5.78; $P = 0.04$; Table

4).

When the effectiveness of atorvastatin and pravastatin were examined, the event rates were similar (n = 13, 36.1% vs. n = 13, 39.4%, respectively, $P = 0.78$). Furthermore, there were no differences in dROM or BAP levels between the atorvastatin and pravastatin groups during the 2 year follow-up period (Figure 4A, B).

Discussion

To our knowledge, previous clinical studies have not attempted to identify the long-term oxidative stress levels in patients with STEMI after PCI. Previous studies have reported that peripheral oxidative stress markers, including dROM,[17,18] are elevated in AMI patients and are strongly correlated with an increased risk of CV events after an AMI.[19] However, in these studies, oxidative stress levels were evaluated only at admission or after a relatively short follow-up period, and a long-term follow-up of oxidative stress levels and their association with CV events was not investigated. Our major findings, derived from a 2 year follow-up of patients with STEMI, are as follows: (1) Although similar baseline dROM and BAP levels were noted in patients with or without CV events, temporal decreases in 6-month BAP levels occurred concomitantly with the occurrence of the cardiac events and the 6-month BAP levels, but not the dROM levels, were lower in patients with CV events than those without; (2) a decreased 6 month BAP level was an independent and significant predictor of long-term CV events after STEMI.

Oxidative stress is linked to increase in age, hypertension, high levels of LDL-C, heart failure, diabetes mellitus, smoking, and impaired renal function, all of which are associated with STEMI.[1,2] However, during the study period, no differences in these comorbidities were noted between patients with and without CV events (data not shown). Additionally, in contrast to

previous studies,[17,18] the baseline dROM and BAP levels were similar between patients with and without CV events and we did not find that baseline dROM or BAP levels could serve as biomarkers for predicting long-term CV risk outcomes after STEMI. However, the 6 month BAP levels, but not dROM levels, were significantly lower in patients with CV events than in those without such events. Furthermore, a decreased BAP level was an independent and significant predictor of CV events in STEMI patients who underwent successful PCI. These results suggest that serial measurements of BAP levels may help predict long-term CV events after STEMI. Our results additionally suggest that oxidative stress, by reducing antioxidant defenses rather than by pro-oxidant generation, might be associated with CV events after STEMI.

In the current study, 73.1% of the CV events in STEMI patients occurred from 6 to 10 months after the primary PCI, and few events were observed from 12 to 24 months. Interestingly, temporal decreases in BAP levels occurred concomitantly with the occurrence of CV events, and intergroup differences were not noted in the 12 and 24 month dROM and BAP levels between patients with and without CV events. However, whether this relationship is causative or resultant remains unclear. In addition, 89.5% of CV events occurring 6-10 months after the primary PCI consisted of PCIs or coronary artery bypass grafting surgery for restenosis after bare-metal stent deployment and the major pathogenesis underlying these restenosis may be explained by oxidative stress-induced neointimal formation.[7,8,20,21]

Since, to our knowledge, no previous prospective, randomized clinical study has identified the difference between the effects of atorvastatin and pravastatin on oxidative stress levels in STEMI patients, we investigated the effect of different statins on oxidative stress levels and CV events in STEMI patients. This substudy comparing the effects of different statins found no differences in dROM and BAP levels between the atorvastatin and pravastatin groups during the

2 year follow-up period. Nor was there any significant difference in the event rates between the 2 groups. The PROVE-IT trial,[22] which was a head-to-head comparison of lipid-lowering therapy with atorvastatin and pravastatin, showed that lipid lowering with lipophilic atorvastatin at 80 mg/day provided greater protection against death and CV events than lipid lowering with hydrophilic pravastatin at 40 mg/day in patients with acute coronary syndrome; however, the results reflected the difference in LDL-C levels achieved during follow-up (62 vs. 95 mg/dL) rather than the difference in the water solubility of the statin and the doses used exceeded the clinical doses administered in Japan. Therefore, in the ALPS-AMI study, we investigated lipophilic vs. hydrophilic statins at their most clinically effective doses (in this subanalysis, doses increased to 20 mg/day: n = 10 and n = 15, respectively, $P = 0.20$) at the equal target LDL-C levels, in order to identify differences between their cardioprotective effects in Japanese patients with AMI. In this subanalysis, the reason why the statin type did not affect the oxidative stress levels and CV events in STEMI patients may be the equal target LDL-C levels in the atorvastatin and pravastatin groups, the low doses of statin, or the small sample size and short duration of statin therapy compared with the PROVE-IT[22] trial.

Conclusions

Temporal decreases in BAP levels occurred concomitantly with the occurrence of CV events, suggesting that serial changes in antioxidant capacity, assessed by BAP levels, may serve as a predictive marker for CV events after STEMI.

Study Limitations

This study has several limitations. First, although our results suggest that 6 month BAP levels were lower in patients with CV events than in those without such events and that a

decreased 6 month BAP level was a predictive marker for long-term cardiac events, it remains to be clarified whether the latter is a causative or resultant factor. Second, the oxidative stress markers (dROM and BAP) measured in this study, are not CV-specific. Third, we were unable to exclude the effects of diurnal and dietary variations on oxidative stress at the time of admission because of the difference in the timing of baseline measurements for the STEMI patients. However, no differences were noted in baseline oxidative stress levels between patients with and without CV events. Finally, a relatively small number of patients was examined. Further studies with a larger number of patients are needed to confirm our results.

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Disclosures

The authors have no conflicts of interest to declare.

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Figure Legends

Figure 1. Diacron-reactive oxygen metabolite (dROM) (A) and biological antioxidant potential (BAP) (B) levels at baseline and following successful percutaneous coronary intervention in the overall patient population with ST-segment-elevation myocardial infarction. Values reflect the median and the interquartile range (25^{th}-75^{th} percentiles). *$P < 0.05$ vs. baseline.

Figure 2. Comparison of oxidative stress levels in patients with and without cardiovascular events. Diacron-reactive oxygen metabolite (dROM) (A) and biological antioxidant potential (BAP) levels at baseline and following successful percutaneous coronary intervention in patients with (●) and without (■) cardiovascular events. Values reflect the median and interquartile range (25^{th}-75^{th} percentiles). "*" indicates that the 6 month BAP levels in patients with cardiovascular events were significantly lower than in those without such events.

Figure 3. Biological antioxidant potential (BAP) levels as a predictor of cardiovascular events after ST-segment-elevation myocardial infarction. (A) The area under the receiver operating characteristic curve for the 6 month BAP levels predicting the primary endpoints was 0.659 (95% CI, 0.528–0.791; sensitivity, 0.500; specificity, 0.759; $P = 0.035$). The optimal cut-off 6-month BAP level was 2718 μmol/L. (B) Kaplan-Meier analysis for all of the primary endpoints in patients with and without a decreased 6 month BAP level (BAP levels ≤2718 μmol/L).

Figure 4. Comparison of oxidative stress levels in the atorvastatin- and pravastatin-treated groups. Diacron-reactive oxygen metabolite (dROM) (A) and biological antioxidant potential (BAP) levels at baseline and following successful percutaneous coronary intervention in the atorvastatin (●) and pravastatin (■) treated groups. Values reflect the median with the interquartile range (25^{th}-75^{th} percentiles). No difference was noted in the dROM and BAP levels between the atorvastatin and pravastatin groups during the study period.

Table 1. Baseline characteristics of the patients with and without cardiovascular events

	Event (+) (n = 26)	Event (–) (n = 43)	*P*
Age (years)	68.0 ± 10.7	64.6 ± 11.9	0.21
Male (%)	21 (80.8%)	33 (76.7%)	0.69
Body mass index (kg/m^2)	23.5 ± 3.2	23.4 ± 2.9	0.87
eGFR (mL/min/1.73m^2)	74.0 ± 22.6	78.2 ± 19.0	0.41
Total cholesterol (mg/dL)	201 (172–230)	204 (170–238)	0.24
LDL-C (mg/dL)	119 (109–143)	124 (101–151)	0.21
HDL-C (mg/dL)	49 ± 10	50 ± 14	0.58
Triglyceride (mg/dL)	101 (56–142)	105 (57–154)	0.21
Hemoglobin A_{1c} (%)	6.0 (5.8–6.4)	5.9 (5.8–6.1)	0.13
BNP (pg/mL)	53.7 (37.5–89.6)	55.8 (34.3–86.7)	0.34
Smoking (%)	19 (73.0%)	29 (67.4%)	0.98
Length of stent (mm)	20.4 ± 7.4	24.0 ± 9.1	0.11
Diameter of stent (mm)	3.1 ± 0.4	3.3 ± 0.5	0.16
Medications			
ACEI/ARBs (%)	8 (22.2%)	9 (27.3%)	0.84
β-blockers (%)	7 (19.4%)	7 (21.2%)	0.89
Statin (%)	26 (100%)	43 (100%)	1.0

Data are presented as mean ± SD or median with interquartile ranges (25^{th}–75^{th} percentiles). *P* value: significance of difference between patients with or without cardiovascular events. eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers

Table 2. Baseline patient characteristics of the patients receiving atorvastatin or pravastatin

	Atorvastatin (n = 36)	Pravastatin (n = 33)	*P*
Age (years)	68.4 ± 10.7	64.4 ± 11.7	0.13
Male (%)	28 (77.8%)	26 (78.8%)	0.92
Body mass index (kg/m^2)	23.4 ± 3.3	23.5 ± 2.8	0.88
eGFR (mL/min/1.73m^2)	74.4 ± 18.5	78.2 ± 16.3	0.47
Total cholesterol (mg/dL)	202 (181–231)	203 (178–233)	0.24
LDL-C (mg/dL)	126 (107–146)	125 (104–143)	0.21
HDL-C (mg/dL)	48 ± 12	49 ± 11	0.58
Triglyceride (mg/dL)	103 (54–145)	102 (51–141)	0.21
Hemoglobin A_{1c} (%)	6.0 (5.8–6.2)	5.9 (5.8–6.1)	0.13
BNP (pg/mL)	54.7 (24.5–89.6)	53.8 (22.3–91.8)	0.34
Smoking (%)	25 (69.4%)	23 (69.7%)	0.98
Length of stent (mm)	21.2 ± 7.2	23.1 ± 8.3	0.18
Diameter of stent (mm)	3.2 ± 0.4	3.3 ± 0.5	0.21
Medications			
ACEI/ARBs (%)	8 (22.2%)	9 (27.3%)	0.83
β-blockers (%)	7 (19.4%)	7 (21.2%)	0.86
Statin (%)	36 (100%)	33 (100%)	1.0
Endpoint			
All	13 (37.7%)	13 (39.4%)	0.78
Death	3 (8.3%)	1 (3.0%)	0.35
PCI	8 (22.2%)	9 (27.2%)	0.63
CABG	1 (2.8%)	2 (6.0%)	0.50
CHF	1 (2.8%)	1 (3.0%)	0.95

Data are presented as mean ± SD or median with interquartile ranges (25^{th}–75^{th} percentiles). *P*

value: significance of difference between patients receiving atorvastatin or pravastatin. eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers; PCI, percutaneous coronary intervention: CABG, coronary artery bypass grafting surgery; CHF, congestive heart failure

Table 3. 24-month characteristics of the patients receiving atorvastatin or pravastatin

	Atorvastatin (n = 33)	**Pravastatin (n = 32)**	***P***
Body mass index (kg/m^2)	23.9 ± 2.2	22.3 ± 2.0	0.75
eGFR (mL/min/1.73m^2)	66.4 ± 14.6	65.8 ± 15.0	0.51
Total cholesterol (mg/dL)	154 (144–168)	161 (150–172)	0.23
LDL-C (mg/dL)	86 (75–93)	84 (74–101)	0.21
HDL-C (mg/dL)	49 ± 10	47 ± 11	0.54
T**riglyceride (mg/dL)**	100 (83–172)	105 (88–188)	0.23
Hemoglobin A_{1c} (%)	6.2 (6.0–6.6)	6.1 (6.0–6.4)	0.29
BNP (pg/mL)	41.0 (18.2–85.9)	52.7 (28.0–79.3)	0.33
Smoking (%)	2 (6.0%)	2 (6.2%)	0.97
Medications			
ACEI/ARBs (%)	18 (54.5%)	14 (43.8%)	0.38
β-blockers (%)	16 (48.5%)	13 (40.6%)	0.52
Statin (%)	33 (100%)	32 (100%)	1.0

Data are presented as mean ± SD or median with interquartile ranges (25^{th}–75^{th} percentiles). *P* value: significance of difference between patients receiving atorvastatin or pravastatin. eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blockers

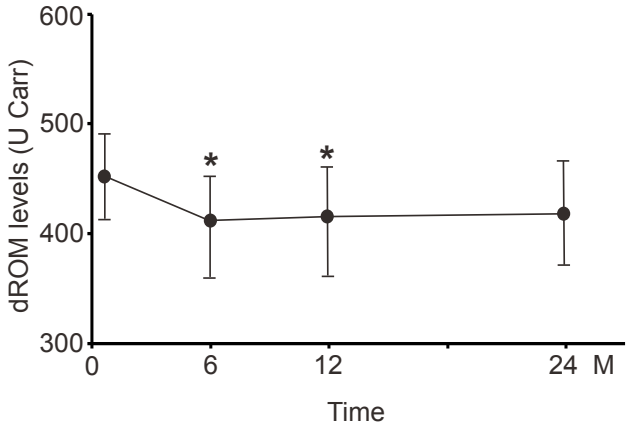
Table 4. Cox predictive model for the endpoints

	HR (95% CI)	*P*
Univariate analysis		
Age (years)	1.00 (0.97–1.03)	0.70
Male	2.46 (0.74–8.14)	0.14
LDL-C (mg/dL)	0.002 (0.980–1.003)	0.15
Hypertension	0.9 (0.43–1.48)	0.79
Diabetes mellitus	1.95 (0.83–4.59)	0.12
Multivessel CAD	1.77 (0.84–3.72)	0.12
eGFR ≤80 ml/min/1.73m^2	2.17 (1.02–4.63)	0.04
6-month BAP ≤2718 μmol/L	2.57 (1.09–6.05)	0.03
Multivariate analysis		
eGFR ≤80 ml/min/1.73m^2	1.78 (0.82–3.85)	0.14
6-month BAP ≤2718 μmol/L	2.45 (1.10–5.78)	0.04

Data are presented as mean ± SD or median with interquartile ranges (25th–75th percentiles). LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ; CAD, coronary artery disease; BAP, biological antioxidant potential ; HR, hazard ratio; CI, confidence interval

Fig. 1A, B

A


600
500
400
300
dROM levels (U Carr)
*
*
0
6
12
24 M
Time

B

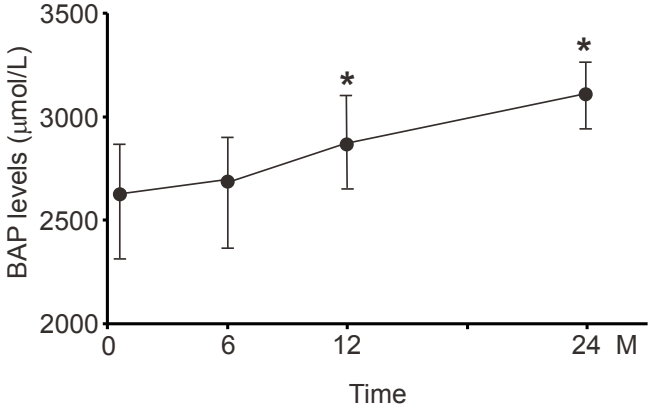

3500
3000
2500
2000
BAP levels (μmol/L)
*
*
0
6
12
24 M
Time

Fig. 2A, B

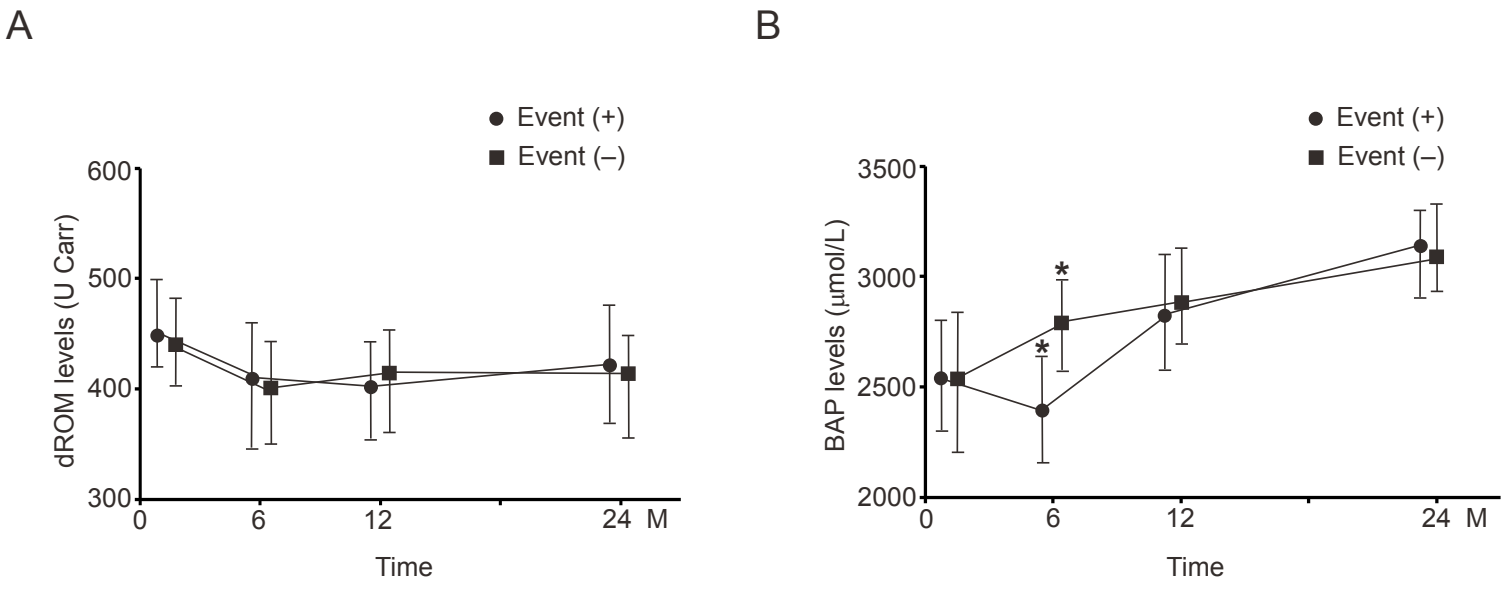
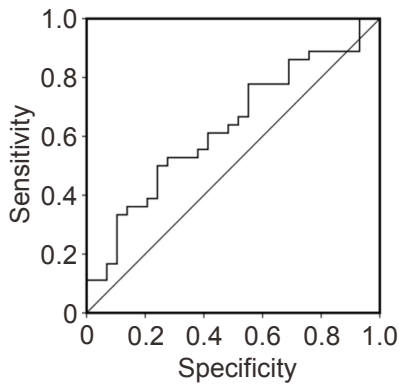

A
Event (+)
Event (–)
dROM levels (U Carr)
600
500
400
300
0
6
12
24 M
Time
B
Event (+)
Event (–)
BAP levels (μmol/L)
3500
3000
2500
2000
*
*
0
6
12
24 M
Time

Fig. 3A, B

A


1.0
0.8
0.6
0.4
0.2
0
Sensitivity
0
0.2
0.4
0.6
0.8
1.0
Specificity

B

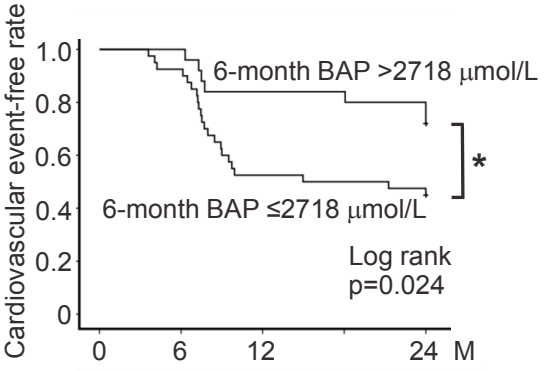
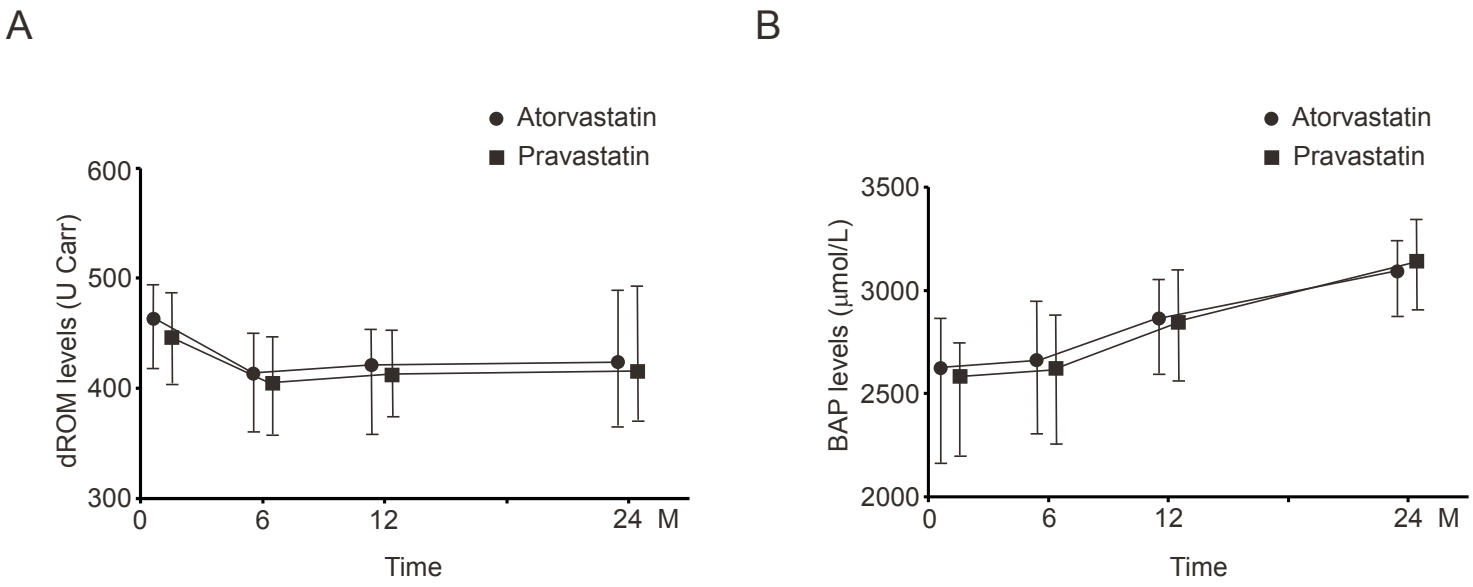

Cardiovascular event-free rate
1.0
0.8
0.6
0.4
0.2
0
6-month BAP >2718 μmol/L
6-month BAP ≤2718 μmol/L
*
Log rank
p=0.024
0
6
12
24 M

Fig. 4A, B


A
Atorvastatin
Pravastatin
dROM levels (U Carr)
600
500
400
300
0
6
12
24 M
Time
B
Atorvastatin
Pravastatin
BAP levels (μmol/L)
3500
3000
2500
2000
0
6
12
24 M
Time