The interaction between endothelin-1 and C-reactive protein and their impact on long-term prognosis after percutaneous coronary interventions

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Abstract

Introduction: Previous studies have demonstrated unfavourable outcomes in coronary artery disease and percutaneous coronary intervention (PCI) patients with high endothelin-1 (ET-1) or high sensitivity C-reactive protein (hs-CRP) levels. The aim of our study was to investigate the impact of pre-procedural ET-1 and hs-CRP levels on major adverse coronary events (MACE) after PCI and to analyse a possible correlation between ET-1 and hs-CRP in this study population.
Material and methods: Eighty consecutive PCI patients with a single de novo, non-occlusive coronary lesion were included. Blood samples were obtained immediately before the procedure. The study endpoint was the occurrence of MACE, which was defined as death (all causes), non-fatal myocardial infarction or repeat coronary revascularization (PCI or surgery).
Results: At the end of the 24 months' follow-up, 28 patients (35%) reached an end-point. We could not observe any correlation between ET-1 and hs-CRP in the overall patient group (r = 0.141, p = 0.213). Neither ET-1 nor hs-CRP levels were found to be predictive for MACE after PCI in multivariate analyses (p = 0.605 and 0.757 respectively).
Conclusions: We could not demonstrate a relationship between pre-procedural ET-1 or hs-CRP levels and MACE at 24 months after successful PCI with single stent implantation to single de novo lesions. This study also could not show any correlation between ET-1 and hs-CRP levels in PCI patients.

Key words: endothelin-1, C-reactive protein, percutaneous coronary intervention, MACE.

Introduction

Previous studies have demonstrated unfavourable outcomes in healthy subjects and coronary artery disease (CAD) patients with high C-reactive protein (CRP) levels, which is a marker of systemic inflammation [1-4]. Endothelin-1 (ET-1), which is a potent vasoactive peptide, producing vasoconstriction, and causes smooth muscle relaxation *via* nitric oxide release, is also related to major adverse coronary events (MACE) in patients with CAD and myocardial injury in chronic ischaemic heart failure patients [5-7]. Increased pre-procedural CRP levels might be associated with poor outcomes after percutaneous coronary interventions (PCI), which was shown in previous studies [8-12]. Also the degree of increase in CRP levels induced by PCI is reported to predict MACE [10]. Although a significant increase in systemic ET-1 levels immediately after coronary stenting was found, no association between ET-1 levels and in-stent restenosis in humans was observed [13]. Because endothelial dysfunction and

inflammation have a serious impact on adverse outcomes after PCI, we hypothesized that pre-procedural ET-1 and high sensitivity CRP (hs-CRP) levels could predict MACE at 24 months after elective PCI with single stent implantation to single non-occlusive *de novo* lesions. Another objective was to analyze a possible correlation between ET-1 and hs-CRP in this study population.

Material and methods

Between April and July 2001, we enrolled 80 prospective and consecutive patients (76.3% male, mean age 57.1 ±9.9 years) who were referred for an elective PCI procedure for a single *de novo*, non-occlusive coronary lesion. All patients underwent PCI for only one lesion, and all patients had a single stent implantation for this target lesion. Exclusion criteria were multilesion PCI, myocardial infarction less than one month, total occlusion, previous PCI or coronary artery bypass surgery, left ventricular ejection fraction < 30%, left bundle branch block and intercurrent inflammatory conditions in the last 6 months. The study was conducted in a single centre. All patients gave written informed consent, and the study was approved by our institutional ethics committee.

Patients were categorized as low and high hs-CRP or ET-1 groups based on whether their hs-CRP or ET-1 level before PCI was above or below the median for each group. Blood samples were obtained by a careful venipuncture immediately before the index procedure. ET-like immunoreactivity was analyzed by radioimmunoassay with the use of commercially available anti-sera (rabbit anti-ET-1 6901, Peninsula Laboratories). Commercially available enzyme immunoassays were used for the determination of plasma concentrations of hs-CRP (Dade Behring Holding GmbH, Liederbach, Germany). The laboratory results were unblinded at the end of the follow-up.

Percutaneous coronary intervention was performed from the femoral artery approach, according to routine clinical practice. A guidewire was positioned distal to the target lesion, and predilatation of the stenosis was performed with a conventional balloon catheter. The stent was deployed at 12 to 16 atm under fluoroscopic control. If further dilatation with larger and/or higher balloon pressure was necessary after stent deployment, the patient was excluded from the study. Treatment with aspirin, at a dose of 300 mg per day, was started before the procedure and continued indefinitely. A loading dose of clopidogrel (300 mg) was also administered before the procedure, followed by 75 mg daily for 4 weeks. Patients received a bolus of 10 000 U of heparin intravenously at the start of the procedure. No patient received glycoprotein IIb/IIIa inhibitors. During PCI, 100-400 µg intracoronary nitroglycerine was given and repeated when necessary. A successful procedure was defined as stent implantation with stenosis of less than 20% of the vessel diameter.

The study endpoint was the occurrence of MACE, which was defined as death (all causes), non-fatal myocardial infarction or repeat coronary revascularization (PCI or coronary artery bypass grafting). Myocardial infarction (MI) was defined as the presence or absence of new pathological Q waves on the surface electrocardiogram plus an increase in creatine kinase (CK) more than twice the upper limit of the normal range with a concomitant increase in its MB isoenzyme, or increase in cardiac troponins above the upper limit of the normal range in the presence of typical symptoms. To meet this end-point criterion, patients who had initially presented with Q-wave MI had to have suffered symptomatic recurrent ST-segment elevation with a rise in CK and/or cardiac troponins and/or angiographic verification of target vessel occlusion. Creatine kinase and cardiac troponin levels were determined systematically for 24 h after the intervention. Target vessel revascularization (TVR) was characterized by repeated PCI or surgical intervention of treated vessels associated with symptoms or objective signs of ischaemia. Twenty four-month follow-up was obtained by reviewing medical records and dedicated telephone interviews.

Discrete variables are reported as counts (percentages) and continuous variables as mean ± SD. To test differences between treatment groups for discrete variables, we used a χ^2 test or Fisher's exact test, as appropriate. Continuous variables were analyzed by *t* test for unpaired samples. Correlation between quantitative variables was assessed by Spearman's correlation coefficient (*r* value). The Kaplan-Meier method was used for cumulative MACE-free survival analysis. The adjusted odds ratios for ET-1, hs-CRP and other CAD risk factors in predicting MACE were calculated by logistic regression analysis. To detect a difference between 2 levels of ET-1 or hs-CRP, for an α of 5% and power of 80%, a minimum of 11 restenosis cases were required. Assuming a dropout rate of 10% and a MACE incidence of 30%, we adopted a sample size of 40 patients in each group. Results were considered significant at the 5% critical level ($p < 0.05$). Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

Results

A total of 80 patients were included prospectively and consecutively in the study with a 100% follow-up at the end of 24 months. The baseline clinical and lesion characteristics are presented in Table I. In 100% of patients a single

Table I. Baseline clinical characteristics

Characteristics	Overall patients (n = 80)	High ET-1 group (n = 40)	Low ET-1 group (n = 40)	p value	High hs-CRP group (n = 40)	Low hs-CRP group (n = 40)	p value
Mean age [years]	57.1 ±9.9	57.5 ±10.3	56.7 ±9.7	0.738	58.4 ±9.5	55.8 ±10.3	0.254
Male sex, n [%]	61 (76.3)	32 (80)	29 (72.5)	0.431	27 (67.5)	34 (85)	0.066
Hypertension, n [%]	46 (57.5)	22 (55)	24 (52.2)	0.651	24 (60)	22 (55)	0.651
Serum LDL cholesterol [mg/dl]	119.6 ±31.3	115.9 ±29.2	123.4 ±33.2	0.285	122.2 ±30.5	117.1 ±32.3	0.473
Diabetes mellitus, n [%]	10 (12.5)	6 (15)	4 (10)	0.737	8 (20)	2 (5)	0.087
Body mass index [kg/m^2]	27.8 ±3.7	27.2 ±3.9	28.3 ±3.5	0.239	28.2 ±4.1	27.3 ±3.4	0.310
Active smoker, n [%]	23 (28.8)	13 (32.5)	10 (25)	0.459	14 (35)	9 (22.5)	0.217
Family history, n [%]	37 (46.3)	18 (45)	19 (47.5)	0.823	16 (40)	21 (52.5)	0.262
Exertional angina, n [%]	40 (50)	25 (62.5)	15 (37.5)	0.025	21 (52.5)	19 (47.5)	0.655
Unstable angina, n [%]	15 (18.8)	6 (15)	9 (22.5)	0.390	9 (22.5)	6 (15)	0.390
Silent ischaemia, n [%]	5 (6.3)	3 (7.5)	2 (5)	1	1 (2.5)	4 (10)	0.359
Prior myocardial infarction, n [%]	37 (46.3)	15 (37.5)	22 (55)	0.116	13 (32.5)	24 (60)	0.014
Baseline medications, n [%]							
β-blocker	13 (16.3)	9 (22.5)	4 (10)	0.225	7 (17.5)	6 (15)	0.762
ACE inhibitor	10 (12.5)	3 (7.5)	7 (17.5)	0.311	5 (12.5)	5 (12.5)	1
Aspirin	80 (100)	40 (100)	40 (100)	NA	40 (100)	40 (100)	NA
Clopidogrel	80 (100)	40 (100)	40 (100)	NA	40 (100)	40 (100)	NA
Statin	44 (55)	22 (55)	22 (55)	1	20 (50)	24 (60)	0.369
Target vessel n [%]							
LMCA	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
LAD	39 (48.8)	16 (40)	23 (57.5)	0.117	23 (57.5)	16 (40)	0.117
CXA	13 (16.3)	7 (17.5)	6 (15)	0.762	6 (15)	7 (17.5)	0.762
RCA	28 (35)	17 (42.5)	11 (27.5)	0.160	11 (27.5)	17 (42.5)	0.160
Lesion type (B2/C)	45 (56.3)	23 (57.5)	22 (55)	0.822	21 (52.5)	24 (60)	0.499
Thrombotic lesion	1 (1.3)	0 (0)	1 (2.5)	1	1 (2.5)	0 (0)	1
Restenotic lesion	0 (0)	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Stent	80 (100)	40 (100)	40 (100)	NA	40 (100)	40 (100)	NA

ACE – angiotensin-converting enzyme, CABG – coronary artery bypass graft surgery, CXA – circumflex artery, ET-1 – endothelin-1, Hs-CRP – high sensitivity C-reactive protein, LAD – left anterior descending coronary artery, NA – not applicable, PCI – percutaneous coronary intervention, RCA – right coronary artery

bare metal stent was implanted for a single de novo, non-occlusive lesion. Angiographic procedural success was obtained in all patients, without any in-hospital complications. At the end of the follow-up 28 patients (35%) reached an end-point. Among the endpoints 3 were deaths (one non-cardiac), 9 were non-fatal MI and 16 were repeat revascularization (15 were target vessel revascularizations).

The median level for pre-procedural ET-1 was 4.35 pg/ml and for pre-procedural hs-CRP was 5.3 mg/l. To evaluate the correlation between ET-1 levels and hs-CRP, we compared these parameters in the overall patient group (7.15 ±6.11 pg/ml and 10.71 ±13.72 mg/l respectively), in patients with (6.73 ±5.24 pg/ml and 10.01 ±10.70 mg/l respectively) and without MACE (7.39 ±6.57 pg/ml and 11.10 ±15.16 mg/l respectively). We could not observe any correlation either in the overall patient group (r = 0.141, p = 0.213), or in the patients without MACE (r = 0.121, p = 0.391), or in patients with MACE (r = 0.171, p = 0.386) (Figure 1). In the overall patient group the mean hs-CRP level was 12.37 ±16.69 mg/l in patients with high ET-1 levels, and 9.05 ±9.84 mg/l in patients with low ET-1 levels, which showed a trend towards higher levels in patients with high ET-1 levels (p = 0.071) (Figure 2).

In patients with MACE the ET-1 level was 6.73 ±5.24 pg/ml, and 7.39 ±6.57 pg/ml in MACE-free patients, which was statistically insignificant (p = 0.651). hs-CRP levels were 10.01 ±10.70 mg/l in patients with MACE and 11.10 ±15.16 mg/l in patients without MACE, which also was not statistically different (p = 0.736) (Figure 3). In patients with high ET-1 levels the incidence of MACE was 12 (30%), whereas it was 16 (40%) in the low ET-1 group (p = 0.348). MACE incidence was 15 (37.5%) in high hs-CRP patients, and 13 (32.5%) in the low hs-CRP group, which also was not statistically significant (p = 0.639). Among the endpoints, incidence of death showed a higher trend in patients with low compared to high ET-1 levels (7.5 and 0% respectively, p = 0.241) (Table II). Kaplan-Meier event-free survival curves are presented in Figure 4. The event rates were similar in both high or low ET-1 groups, and high or low hs-CRP groups (p values 0.533 and 0.575 respectively).

Neither ET-1 nor hs-CRP levels, nor other conventional CAD risk factors, were found to be predictive for MACE after PCI in multivariate analyses, which are presented in Table III (p value for all variables > 0.05).

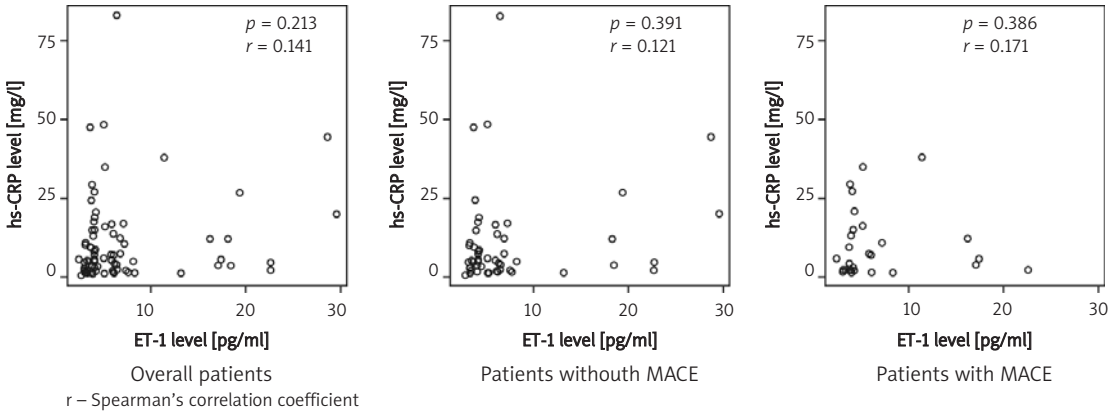

Figure 1. Correlation between ET-1 and hs-CRP levels among overall patients, patients with or without MACE

Table II. Comparison of endpoints among patients with low vs. high ET-1 or hs-CRP levels

Endpoints	ET-1 high (n = 40)	ET-1 low (n = 40)	p value	hs-CRP high (n = 40)	hs-CRP low (n = 40)	p value
Death	0 (0%)	3 (7.5%)	0.241	1 (2.5%)	2 (5%)	1
Non-fatal myocardial infarction	5 (12.5%)	4 (10%)	1	6 (15%)	3 (7.5%)	0.481
Target vessel revascularization	7 (17.5%)	8 (20%)	0.775	8 (20%)	7 (17.5%)	0.775
Repeat revascularization	7 (17.5%)	9 (22.5%)	0.576	8 (20%)	8 (20%)	1
Total MACE	12 (30%)	16 (40%)	0.348	15 (37.5%)	13 (32.5%)	0.639

ET-1 – endothelin 1, hs-CRP – high sensitivity C-reactive protein, MACE – major adverse coronary events

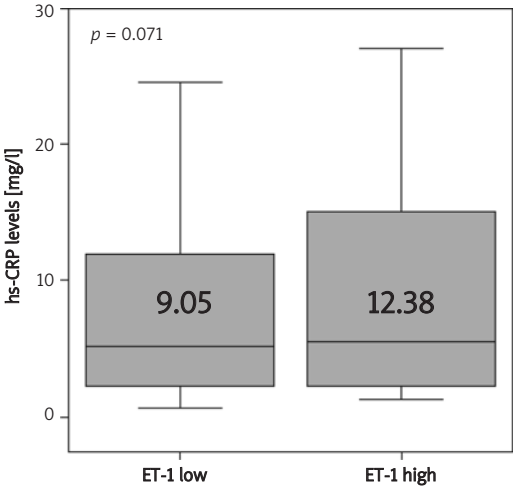

Figure 2. Comparison of hs-CRP levels in patients with high ET-1 levels and low ET-1 levels

Table III. Adjusted odds ratios for MACE prediction at 2 years

	Odds ratio	95% confidence interval	*p* value
Endothelin-1 level	0.977	0.896-1.066	0.605
hs-CRP level	0.994	0.957-1.033	0.757
Age	1.015	0.960-1.074	0.592
Male gender	0.501	0.147-1.706	0.269
Hypertension	1.034	0.360-2.968	0.951
Diabetes	0.793	0.186-3.392	0.755
LDL cholesterol	1.013	0.996-1.031	0.140
Active smoker	1.274	0.396-4.098	0.684
Family history	0.828	0.306-2.240	0.710
Previous MI	1.353	0.438-4.182	0.599

hs-CRP – high sensitive C-reactive protein, LDL – low density lipoprotein, MACE – major adverse cardiac outcomes, MI – myocardial infarction

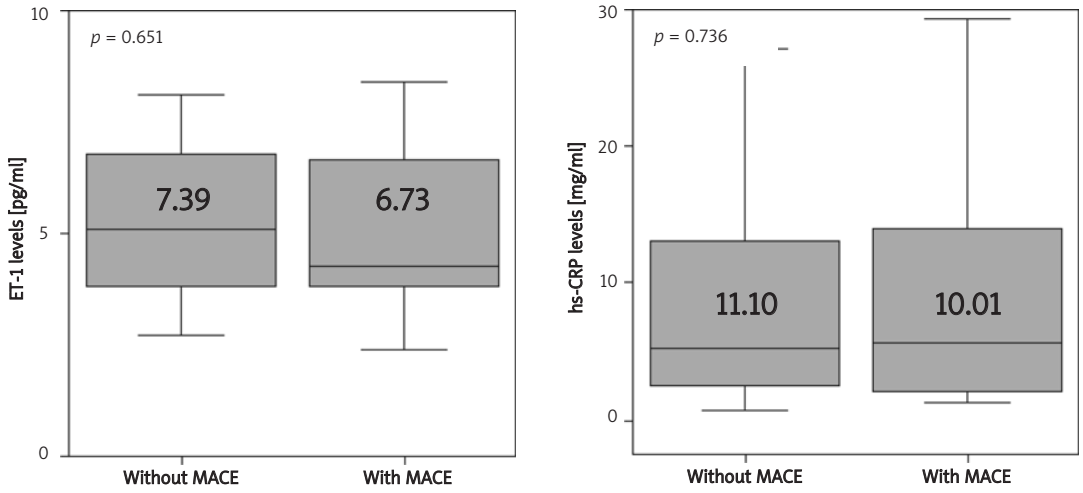

Figure 3. Comparison of ET-1 and hs-CRP levels in patients with or without MACE at 24 months

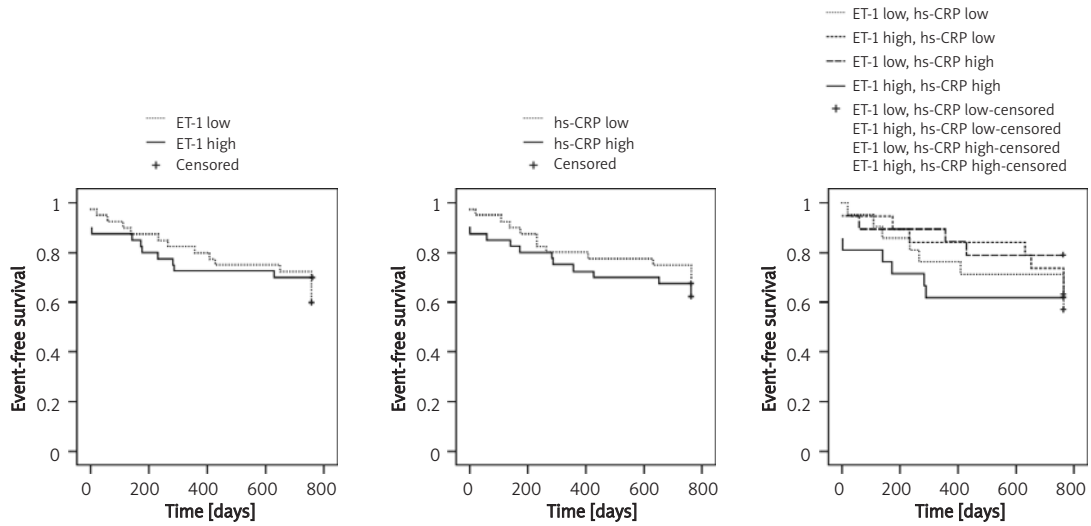

Figure 4. Event-free survival curves of patients with high or low ET-1 or hs-CRP levels

Discussion

To our knowledge this is the first study investigating the correlation between pre-procedural ET-1 and hs-CRP levels and their impact on prognosis in PCI patients to whom a single stent is implanted to a single lesion. C-reactive protein is the most studied inflammatory marker in CAD and PCI patients. Several previous studies have reported CRP levels to be increased in acute coronary syndromes [14-16]. It has also been found to be associated with restenosis or MACE after PCI, whereas some other studies could not show a relationship [12, 17-19]. We also could not demonstrate a relationship between hs-CRP levels and MACE in PCI patients. The mechanisms by which elevated CRP levels lead to adverse coronary events is still not clear. C-reactive protein is synthesised and secreted by hepatocytes in response to several cytokines [20]. C-reactive protein levels reflect the degree of underlying inflammation, which in turn is known to be related to restenosis [21]. In addition, CRP has been shown to bind to damaged tissues and to act synergistically with lipopolysaccharide in the activation of endothelial cells and to induce tissue factor production by monocytes [22-24]. Publications have reported a relationship with both pre-procedural and post-procedural CRP levels and also with the increase of CRP levels after PCI. In our study we focused on pre-procedural biomarker analysis, which might be considered more important for risk stratification of PCI patients before the procedure.

ET-1, which is a potent vasoactive peptide, producing vasoconstriction and smooth muscle relaxation *via* nitric oxide release, has been investigated in many animal and clinical studies [5, 25-27]. ET-1 has been shown to increase mitogenic activity on smooth muscle cells and therefore suggested to have an impact on neointimal hyperplasia [25, 28]. ET-1 antagonists have been reported to have beneficial roles in suppressing restenosis [29]. Besides these effects, clinical study results are controversial [13, 30]. We could not demonstrate an association between pre-procedural ET-1 levels and MACE in our study population. Although not statistically significant, we have observed a trend towards a higher incidence of death in patients with low ET-1 levels. Data on the relationship between ET-1 levels and adverse coronary events are controversial. Ruo *et al*. have demonstrated increased death and MI rates in postmenopausal women with coronary artery disease, who had elevated ET-1 levels. Whereas in another study by Hedman *et al*., although not statistically significant, patients who had an occluded coronary bypass graft had lower ET-1 levels [26]. Our finding might be coincidental and should be verified in larger studies.

Several previous studies have reported the influence of aspirin, clopidogrel, calcium channel blockers and β-blockers on endothelin release and its vasomotor actions [31-34]. Approximately 15-25% of our patients were on β-blocker treatment, and the incidences of β-blocker use were similar between groups. In addition, all patients were given aspirin and a loading dose of clopidogrel the same day of the procedure after blood sampling. Therefore pre-procedural endothelin levels might not be affected by medications in our study.

There is insufficient data on the correlation between ET-1 and hs-CRP in CAD and PCI patients. In our study we have shown the absence of a correlation between these two biomarkers, which are known to be important on their own in several pathways of restenosis and mechanisms to provoke coronary events.

Although the study was sufficiently powered to make a conclusion on the possible impact of pre-procedural ET-1 and hs-CRP on MACE after PCI, this study should be verified in a larger patient population. One factor affecting our results might be the selection of patients who only had a single target lesion. We excluded multivessel disease to provide a more homogeneous patient population, whereas multivessel disease could have a cumulative effect on pre-procedural ET-1 and hs-CRP increase, which might have a greater influence on MACE prediction. Post-procedural levels of ET-1 and hs-CRP or the increase after the procedure could be more important in the pathogenesis of restenosis and MACE. We also could not use drug-eluting stents in our study population because they were not available in our country during the study enrolment period. This study could be repeated in patients with multivessel disease, measuring post-procedural ET-1 and hs-CRP levels.

In conclusion, we could not demonstrate a relationship between pre-procedural ET-1 or hs-CRP levels and MACE at 24 months after successful PCI with single stent implantation to single de novo lesions. This study also could not show any correlation between ET-1 and hs-CRP levels in PCI patients.

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