

# Pentraxin 3 might be better prognostic serum marker than IL-6, IL-10, and high-sensitivity C-reactive protein for major adverse cardiovascular events in patients with ST-elevation myocardial infarction after bare-metal stent implantation

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### ABSTRACT

**الأهداف:** تقييم القيمة التكهنية للبنتراكسين 3 (PTX3) في المرضى الذين يعانون من احتشاء عضلة القلب (STEMI) بعد زرع الدعامات المعدنية العارية (BMS).

**المنهجية:** أجريت هذه الدراسة المستقبلية، تم تحديد PTX3، إنترلوكين IL-6، IL-10، بروتين سي التفاعلي عالي الحساسية (hsCRP)، وتروبونين القلبي (cTnI) لقيم البلازما قبل وبعد 24 ساعة من زرع BMS في 97 من المرضى المسجلين على التوالي مع STEMI الذين تم قبولهم في المركز السريري الجامعي توزلا، توزلا، البوسنة والهرسك خلال الفترة من فبراير 2016م وفبراير 2017م. كما تم متابعة المرضى لمدة 24 شهرا لتقييم الأحداث السلبية للقلب والأوعية الدموية (MACEs).

**النتائج:** بعد 24 ساعة من التدخل التاجي عن طريق الجلد (PCI)، ازدادات قيم البلازما بشكل إحصائي لكل من PTX3، IL-6، hsCRP، hsCRP و cTnI؛ وانخفضت مستويات IL-10 بشكل كبير مقارنة مع القيم المحددة قبل PCI. المرضى الذين يعانون من أحداث سلبية للقلب والأوعية الدموية (MACEs) كانت مستويات بلازما PTX3 أعلى بكثير في 24 ساعة بعد BMS-PCI من المرضى الذين يعانون من MACEs. كان المرضى الذين كانت قيم البلازما PTX3 لديهم أكثر من أو تساوي 5.042 نانوغرام/مل لديهم مخاطر عالية لـ MACEs من المرضى الذين لديهم مستويات PTX3 أقل من 5.042 نانوغرام/مل. أظهرت مستويات البنتراكسين 3 ارتباطات قوية وهامة مع IL-6 ومستويات IL-10. أظهرت مستويات بنتراكسين ارتباط قوي ومهم إحصائي مع IL-6 ومستويات IL-10. بنتراكسين، hsCRP، cTnI، IL-6، و IL-10، وليس مع مستويات hsCRP الذي لم يظهر أي ارتباط مستقل مع MACEs وفقا لتحليل انحدار كوكس متعدد المتغيرات.

**الخلاصة:** TPTX3 قد يكون علامة منذره للمصل أفضل من IL-6، IL-10، أو حساسية عالية CRP للـ MACEs بعد BMS-PCI. قد يساعد على جعل التقسيم الطبقي للمخاطر أفضل لهؤلاء المرضى الذين يخضعون لـ BMS-PCI.

**Objectives:** To assess the prognostic value of pentraxin 3 (PTX3) in patients with ST-elevation myocardial infarction (STEMI) after bare-metal stent (BMS) implantation.

**Methods:** In this prospective study, PTX3, interleukin (IL-6), IL-10, high-sensitivity c-reactive protein (hsCRP), and cardiac troponin I (cTnI) plasma values were determined before and 24 hours after BMS implantation in 97 consecutively enrolled patients with STEMI who were admitted to University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina between February 2016 and February 2017. Patients were followed for 24 months to assess major adverse cardiovascular events (MACEs).

**Results:** At 24 hours after percutaneous coronary intervention (PCI), plasma values of PTX3, IL-6, hsCRP, and cTnI were significantly increased; and IL-10 levels were significantly decreased compared with the values determined before PCI. Patients with MACEs had significantly higher plasma PTX3 levels at 24 hours after BMS-PCI than in patients without MACEs. Patients with PTX3 plasma values  $\geq 5.042$  ng/ml had a significantly higher risk of MACEs than patients with PTX3 levels  $< 5.042$  ng/mL. Pentraxin 3 levels exhibited strong and significant correlations with IL-6 and IL-10 levels. Pentraxin 3, cTnI, and IL-6, but not hsCRP levels have showed independent association with MACEs, according to the multivariate Cox regression analysis.

**Conclusion:** Pentraxin 3 might be better serum prognostic marker than IL-6, IL-10 or high sensitivity CRP for MACEs after BMS-PCI. It might help to make better risk stratification of those patients who are undergoing BMS-PCI.

*Saudi Med J 2019; Vol. 40 (12): 1202-1208*  
*doi: 10.15537/smj.2019.12.24737*

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*Received 12th July 2019. Accepted 11th November 2019.*

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Pentraxin 3 (PTX3) along with C-reactive protein (CRP) and other small proteins belongs to the group named Pentraxins. Many different cells in the human body secrete PTX3 as a result of different pro-inflammatory stimuli.<sup>1</sup> Local inflammatory response in the vessel wall has been reported to be an inducer of severe complications in patients with ST-segment elevation or non-ST-segment elevation myocardial infarction.<sup>2</sup> It has been reported that increased PTX3 plasma value is a good prognostic serum marker for coronary artery disease.<sup>3,4</sup> Myocardial revascularization by percutaneous coronary intervention (PCI) using deployment either bare-metal stent (BMS) or drug eluted stent (DES) is gold standard in treatment of ischemic heart disease. Trauma of artery wall by PCI procedures, local inflammation is developed and it causes major adverse cardiovascular events (MACE).<sup>5,6</sup> Over the past years, several research studies have reported that PTX3 plasma value is increased after myocardial revascularization carried out by PCI,<sup>7-9</sup> and it is associated with MACEs.<sup>10</sup> Pentraxin 3 plasma value might be better local inflammatory marker than high-sensitivity (hs) CRP for predicting long-term MACEs in patients underwent to DES-PCI.<sup>10</sup>

Increased interleukin-6 (IL-6) plasma value is good predictor of cardiovascular complications such as myocardial infarction, stent thrombosis, and cardiac death after DES-PCI in patients with unstable angina pectoris who did not receive antihyperlipidemic treatment.<sup>11</sup> Increased IL-6 plasma values and a lower sIL-6R/IL-6 ratio suggest decreased ejection fraction and larger size of infarct in a short period of time after myocardial infarction with ST-elevation.<sup>12</sup> In patients who received clopidogrel increased IL-6 plasma values are associated with either early or late stent thrombosis, indicating that cytokines are involved in the development of stent thrombosis.<sup>13</sup> Decreased plasma IL-10 levels in patients who developed in-stent restenosis suggest that it might play some important anti-inflammatory role in the development of in-stent restenosis.<sup>14</sup> There is an association between plasma values of IL-10, MMP, IL-18 and the incidence of in-stent restenosis in patients who underwent PCI.<sup>15</sup>

In our study we assessed whether PTX3 plasma level is better long-term prognostic serum marker for major adverse cardiovascular events than IL-6, IL-10, hsCRP

and cardiac troponin I (cTnI) plasma values after BMS implantation in patients with STEMI.

**Methods.** Ninety-seven patients who had STEMI were consecutively enrolled and treated by PCI using BMS at the Department of Cardiology, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina between February 2016 and February 2017. The committee of ethics issues of research studies at University Clinical Center Tuzla has approved this study. All patients voluntarily agreed to be included in this study and they signed informed consent. In this study, patients with other type of coronary artery disease, renal failure, liver end stage disease, severe pulmonary disease, systemic acute or chronic inflammation and malignant tumors were not included. Clinical characteristic such as: number of stents, length of stent, diameter of stent, prior type of myocardial revascularization, hypertension, hyperlipidemia, age, diabetes mellitus, gender, left ventricular ejection fraction, Killip class, body mass index, and smoking status have been obtained by patient interviews at hospital admission and in-clinical records.

Whole venous blood samples have been taken before and 24 hours after BMS-PCI in a tube with ethylenediaminetetraacetic acid and right away after PCI centrifuged at 2000 x g for 15 minutes at a room temperature. Plasma samples were frozen at -80°C and kept until certain laboratory test. Pentraxin 3, IL-6, and IL-10 plasma values were determined using standard ELISA test.

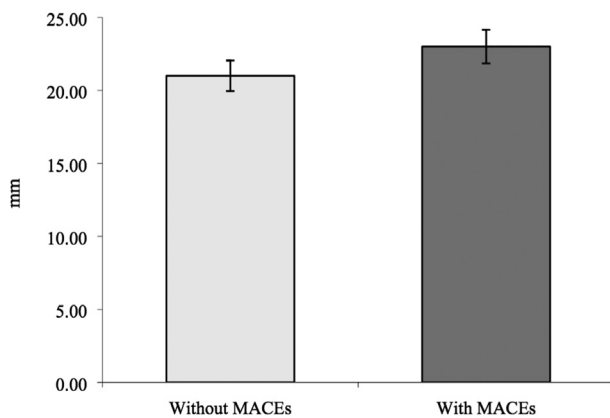
Plasma concentrations of hsCRP, cTnI, creatine kinase-myocardial band, glucose, creatinine were measured by using standard routine methods. All patients after BMS PCI have been followed-up for 24 months to be assessed for MACEs. Follow-up after BMS-PCI has been carried out by patient's visits or phone interviews at 1, 6, 12, 18, and 24 months. All BMS-PCIs were performed by a co-author, and all clinical and laboratory data have been brought together by another co-author. Both of these investigators were blinded to PTX-3, hsCRP, IL-6 and IL-10 values.

**Statistical analysis.** Student's test, Mann-Whitney u-test, Fisher's exact test, Chi-square test and linear regression depend on type of variables have been analyzed by the Statistical Package for Social Sciences, version 25 (IBM Corp, Armonk, NY, USA). To determine prognostic value of clinical and serum marker variables univariate and multivariate Cox proportional hazard regressions have been used. Relative risks (RR) with 95% confidence intervals were reported. Statistical significance of difference was considered relevant if  $p < 0.05$ .

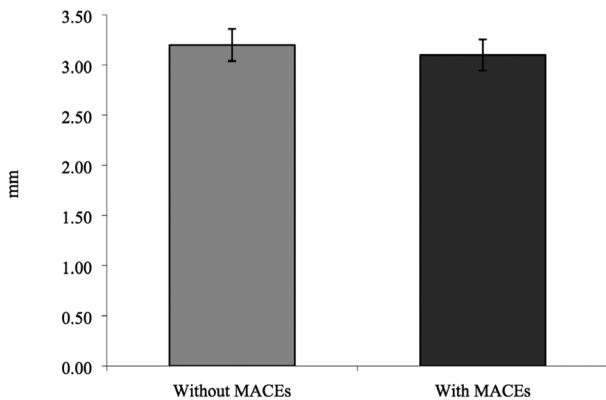
**Disclosure.** Authors have no conflict of interests, and the work was not supported or funded by any drug company.

**Results.** The study group included 97 patients, 71 men (73.2%) and 26 women (26.8%) (mean age  $61.8 \pm 5.7$  years). As shown in Figures 1 and 2, to all patients was deployed only one stent, and means of length ( $23 \pm 1.4$  versus [vs]  $21 \pm 1.9$  mm;  $p > 0.05$ ) and diameter of stent ( $3.1 \pm 0.2$  vs  $3.2 \pm 0.4$  mm;  $p > 0.05$ ) did not significantly differ.

Over 24 months of follow-up, MACEs occurred in 19 (19.6%) patients, including 5 (5.2%) cardiac deaths, 3 (3.1%) nonfatal myocardial infarction and 11 (11.3%) target vessel revascularization. First, we tested whether PTX3 plasma value changed after BMS-PCI and then assessed the association between PTX3 plasma values and MACEs after BMS-PCI. As shown in Table 1, PTX3 plasma values determined 24 hours after BMS-PCI were significantly increased comparing



**Figure 1** - Mean stent length deployed during bare-metal stent-percutaneous coronary intervention in ST-elevation myocardial infarction. MACEs - major adverse cardiovascular events



**Figure 2** - Mean stent diameter deployed during bare-metal stent-percutaneous coronary intervention in ST-elevation myocardial infarction. MACEs - major adverse cardiovascular events

them with the values determined before BMS-PCI ( $4.96 \pm 0.78$  vs  $3.41 \pm 0.55$  ng/mL,  $p < 0.001$ ). Pentraxin 3 plasma values before BMS-PCI did not show significant change among patients with and without MACEs ( $3.52 \pm 0.43$  vs  $3.36 \pm 0.57$  ng/mL,  $p = 0.366$ ). Nineteen patients with MACEs showed significantly increased PTX3 plasma values 24 hours after BMS-PCI than those in the 78 patients without MACEs ( $6.42 \pm 0.27$  vs  $4.61 \pm 0.38$  ng/mL,  $p < 0.001$ ).

Interleukin-6 plasma values determined 24 hours after percutaneous coronary intervention were significantly increased compared with the values determined before BMS-PCI ( $8.11 \pm 0.63$  vs  $6.78 \pm 0.39$  pg/mL,  $p = 0.032$ ). Interleukin-6 plasma values before percutaneous coronary intervention did not show significant among patients with and without MACEs ( $6.95 \pm 0.37$  vs  $6.59 \pm 0.74$  pg/mL,  $p = 0.471$ ). In patients who had MACEs IL-6 plasma values were significantly increased 24 hours after BMS-PCI than those in patients without MACEs ( $8.63 \pm 0.31$  vs  $7.81 \pm 0.69$  pg/mL,  $p = 0.048$ ).

Interleukin-10 plasma values determined 24 hours after BMS-PCI were significantly decreased compared with the values determined before BMS-PCI ( $19.44 \pm 0.82$  vs  $20.73 \pm 0.13$  pg/mL,  $p = 0.041$ ), and IL-10 plasma values before BMS-PCI did not show significant change among patients with and without MACEs ( $20.86 \pm 0.52$  vs  $20.56 \pm 0.23$  pg/mL,  $p = 0.604$ ). However, patients with MACEs showed significantly decreased IL-10 plasma values 24 hours after BMS-PCI than those in patients without MACEs ( $18.28 \pm 0.39$  vs  $19.63 \pm 0.85$  pg/mL,  $p = 0.039$ ).

Patients with MACEs presented higher concentrations of hsCRP after PCI than those in patients without MACEs ( $4.84 \pm 0.46$  vs  $4.08 \pm 0.29$  ng/mL,  $p = 0.017$ ). However, a significant difference in the plasma hsCRP concentrations before PCI was not observed between patients with MACEs and patients without MACEs ( $3.61 \pm 0.77$  vs  $3.39 \pm 0.59$  ng/mL,  $p = 0.708$ ).

Table 2 shows increased cTnI plasma values in patients with MACEs after BMS-PCI ( $p < 0.001$ ) compared to those without MACEs. Increased prevalence of Killip class  $> II$  ( $p = 0.010$ ) and left ventricular ejection fraction  $< 50\%$  ( $p = 0.016$ ) were found in patients with MACEs.

Patients with PTX3 plasma values  $\geq 5.042$  ng/mL had increased cTnI plasma value ( $23.72 \pm 0.62$  vs  $19.26 \pm 0.48$  ng/mL,  $p < 0.001$ ) and increased prevalence of left ventricular ejection fraction  $< 50\%$  ( $p = 0.041$ ) compared to patients with PTX3 plasma values  $< 5.042$  ng/mL (Table 3).

Table 4 shows significantly higher risks of MACEs ( $p = 0.011$ ) and TVRs ( $p = 0.015$ ) for patients if PTX3

plasma values  $\geq 5.042$  ng/mL compared to patients with PTX3 plasma values  $< 5.042$  ng/mL.

**Assessment of predictors of major adverse cardiovascular events.** It was observed that PTX3 plasma values, IL-6, IL-10, hsCRP, diabetes mellitus, hypertension, age, and Killip class  $>II$  showed significant association with MACEs.

Using multivariate Cox regression analysis, it was observed that PTX3 plasma values, cTnI plasma values, IL-6, IL-10, smoking, hyperlipidemia, age, and hypertension showed independent association with MACEs (Table 5).

Pentraxin 3 plasma values determined 24 hours after BMS PCI displayed strong and significant positive

correlations with IL-6 and negative correlations with IL-10 plasma values. However, PTX3 plasma values exhibited weak, but significant correlations with hsCRP and cTnI (Table 6).

**Discussion.** In this study, we observed findings described below in patients with STEMI after BMS implantation: a) PTX3 plasma values increased significantly 24 hours after BMS-PCI compared with values determined before implantation; b) patients with MACEs presented a greater increase in PTX3 plasma values after PCI than that in patients without MACEs; c) patients who had PTX3 plasma values after BMS-PCI exceeding 5.042 ng/mL showed increased

**Table 1 -** Comparison of serum inflammatory markers measured 24 hours after and after BMS-PCI in all patients with STEMI, before PCI in the groups with and without MACEs, and at 24 hours after PCI in the groups with and without MACEs.

Serum inflammatory marker	All Patients			Before PCI			24 hours after PCI		
	Before PCI	After PCI	P-value	Without MACEs	With MACEs	P-value	Without MACEs	With MACEs	P-value
PTX-3 (ng/mL)	3.41±0.55	4.96±0.78	<0.001	3.36±0.57	3.52±0.43	0.366	4.61±0.38	6.42±0.27	<0.001
IL-6 (pg/mL)	6.78±0.39	8.11±0.63	0.032	6.59±0.74	6.95±0.37	0.471	7.81±0.69	8.63±0.31	0.048
IL-10 (pg/mL)	20.73±0.13	19.44±0.82	0.041	20.56±0.23	20.86±0.52	0.604	19.63±0.85	18.28±0.39	0.039
hsCRP (ng/mL)	3.53±0.46	4.18±0.84	0.026	3.39±0.59	3.61±0.77	0.708	4.08±0.29	4.84±0.46	0.017

BMS-PCI - bare-metal stent-percutaneous coronary intervention, STEMI - ST-elevation myocardial infarction, MACEs - major adverse cardiovascular events, IL - interleukin

**Table 2 -** Clinical characteristics of patients with and without MACEs

Variables	All patients (n=97)	Without MACEs (n=78)	With MACEs (n=19)	P-value
Age (years)	67.1±7.6	64.4±8.3	71.6±6.9	<0.001
LVEF <50%	30 (30.9)	22 (28.2)	8 (42.1)	0.016
Diabetes mellitus	19 (19.6)	15 (19.2)	4 (21.1)	0.566
Hyperlipidemia	39 (40.2)	31 (39.7)	8 (42.1)	0.739
cTnI (ng/mL)	21.53±0.38	18.28±0.62	26.04±0.92	<0.001
Current smoker	33 (34.0)	26 (33.3)	7 (36.8)	0.457
Hypertension	37 (38.1)	29 (37.2)	8 (42.1)	0.339
Killip class $>II$	34 (35.1)	25 (32.1)	9 (47.4)	0.010

Values are presented as numbers and percentages (%). MACEs - major adverse cardiovascular events, cTnI - cardiac troponin I, LVEF - left ventricular ejection fraction

**Table 3 -** Clinical characteristics of patients stratified according to the median PTX3 level measured 24 hour after PCI.

Characteristics	PTX3 < 5.042 ng/mL (n=51)	PTX3 $\geq 5.042$ ng/mL (n=46)	P-value
Age (years)	67.3±5.3	66.8±4.2	0.483
LVEF <50%	13 (25.5)	17 (36.9)	0.041
Diabetes mellitus	9 (17.6)	10 (21.7)	0.063
Hyperlipidemia	20 (39.2)	19 (41.3)	0.820
cTnI (ng/mL)	19.26±0.48	23.72±0.62	<0.001
Current smoker	17 (33.3)	16 (34.8)	0.174
Hypertension	20 (39.2)	17 (36.9)	0.396
Killip class $>II$	18 (35.3)	16 (35.5)	0.762

Values are presented as numbers and percentages (%). PTX3 - pentraxin 3, PCI - percutaneous coronary intervention, cTnI - cardiac troponin I, LVEF - left ventricular ejection fraction

risk for major adverse cardiovascular events; d) PTX3 plasma values strongly and significantly correlated with IL-6 or IL-10 plasma values; e) using univariate Cox regression analysis, PTX3, IL-6, IL-10, hsCRP, diabetes mellitus, hypertension, age, and Killip class >II significantly correlated with MACEs; f) PTX3, cTnI, IL-6, IL-10, smoking, hyperlipidemia, hypertension, and age, showed independent association with major cardiovascular adverse events using multivariate Cox regression test.

Based on these findings, PTX3 plasma values determined after BMS-PCI could be better prognostic serum marker of long-term MACEs than IL-6, IL-10 and hsCRP plasma values in patients who had with

ST-segment elevation myocardial infarction after BMS-PCI. Determination of PTX3 plasma value may help in creating better risk classification of patients who had STEMI undergoing BMS-PCI and may improve management of high-risk patients with STEMI after BMS-PCI.

In our study we have found an independent association between PTX3 plasma values and long-term major cardiovascular complications in patients who had STEMI after BMS-PCI. Several studies have evaluated predictive significance of PTX3 plasma values in patients who had myocardial infarction with ST-elevation. According to Tomandlova et al,<sup>16</sup> PTX3 plasma values determined 24 hours after myocardial infarction with

**Table 4 -** Risk stratification of patients with STEMI after BMS-PCI based on elevated PTX3 levels (greater than the median value of 5.042 ng/mL).

PTX3 (ng/mL)	Overall (n=97)	≥5.042 (n=46)	<5.042 (n=51)	P-value
MACEs	19 (19.6)	14 (30.4)	5 (9.8)	0.011
Cardiac death	5 (5.2)	4 (8.7)	1 (1.9)	0.134
Nonfatal myocardial infarction	3 (3.1)	2 (4.3)	1 (1.9)	0.498
TVR, n (%)	11 (11.3)	9 (19.6)	2 (3.9)	0.015

Values are presented as numbers and percentages (%). STEMI - ST-elevation myocardial infarction, BMS-PCI - bare-metal stent-percutaneous coronary intervention, MACEs - major adverse cardiovascular events, PXT3 - pentraxin 3, MI myocardial infarction, TVR - target vessel revascularization

**Table 5 -** Univariate and multivariate Cox regression analyses of MACEs in patients with STEMI after BMS.

Variables	Univariate analysis RR (95% CI)	P-value	Multivariate analysis RR (95% CI)	P-value
LVEF <50%	1.458 (0.995-2.338)	0.320	1.162 (0.659-1.902)	0.682
Killip class >II	1.586 (1.040-2.598)	0.025	1.068 (0.629-1.706)	0.704
Pentraxin-3	3.012 (1.720-5.169)	0.000	2.402 (1.392-4.286)	0.000
Interleukin-6	2.572 (1.649-4.178)	0.029	2.043 (1.227-3.105)	0.005
Interleukin-10	2.656 (2.263-3.422)	0.044	2.172 (1.481-3.004)	0.006
hsCRP	1.611 (1.453-2.087)	0.004	1.058 (0.976-1.182)	0.597
Cardiac troponin I	0.983 (0.955-1.152)	0.368	1.003 (1.001-1.179)	0.006
Current smoker	1.052 (0.545-1.721)	0.436	1.269 (1.138-1.603)	0.047
Diabetes mellitus,	1.624 (1.074-2.633)	0.005	1.185 (0.596-2.124)	0.542
Hyperlipidemia	1.265 (0.731-1.922)	0.748	1.325 (1.241-1.731)	0.006
Hypertension	1.012 (0.817-1.639)	0.008	1.479 (1.368-1.825)	0.028
Age	1.054 (1.022-1.188)	0.003	1.073 (1.003-1.186)	0.005

MACEs - major adverse cardiovascular events, BMS - bare-metal stent, hsCRP - high-sensitivity c-reactive protein, STEMI - ST-elevation myocardial infarction, LVEF - left ventricular ejection fraction

**Table 6 -** The correlation between pentraxin 3 and interleukin-6, interleukin-10, hsCRP and cTnI levels measured 24 hours after BMS-PCI.

Variables	Interleukin-6	Interleukin-10	hsCRP	cTnI
<i>Pentraxin-3</i>				
r	0.75	-0.64	0.247	0.229
p	0.001	0.002	0.035	0.028

hsCRP - high-sensitivity c-reactive protein, cTnI - cardiac troponin I, BMS-PCI - bare-metal stent-percutaneous coronary intervention

ST-elevation were good prognostic parameter of one month and 12 months mortality or heart failure. Increased PTX3 plasma value at admission in hospital is associated with cardiac death during hospitalization and 2-year mortality regardless of cause in patients who had myocardial infarction with ST-elevation underwent to PCI.<sup>17</sup> In patients with STEMI, PTX3, but not CRP, BNP, CK plasma values is good predictor of 3-month mortality.<sup>18</sup>

Many different cells such as vascular smooth muscle cell, myocardial cells, and others produce PTX3 in place of inflammation as a result of pro-inflammatory stimuli.<sup>1</sup> Vessel wall damage or PCI procedure or both might increase PTX3 plasma values. In the present study, PTX3 plasma values were significantly increased in patients with STEMI 24 hours after BMS-PCI compared with the values determined before the procedure. Several recent studies reported significantly elevated PTX3 plasma values 24 hours after STEMI in patients undergoing primary PCI.<sup>16,18,19</sup> Similar results have been found in patients with non-ST-segment elevation myocardial infarction.<sup>20,21</sup>

Percutaneous coronary intervention induces an inflammatory response and changes in its markers, such as increased levels of PTX3, hsCRP, and IL-6 and decreased IL-10 levels, in patients after PCI predict worse clinical outcomes.<sup>6-8,13-15</sup>

In the present study, using univariate Cox regression analysis, PTX3, IL-6, IL-10, hsCRP, Killip class >II, diabetes mellitus, hypertension, and age showed significant association with MACEs. However, IL-6, cTnI, IL-10, PTX3 plasma values, age, smoking, hyperlipidemia, and hypertension showed statistically independent association with major cardiovascular adverse events using multivariate Cox regression test. Pentraxin-3 has shown strong and significant positive correlation with IL-6 and negative correlation with IL-10) plasma values. However, PTX-3 showed weak correlation with hsCRP and cTnI plasma values. These correlations of PTX3 which is more specific for the cardiovascular system may indicate that PTX3 has better prognostic value.

Over the past years, several studies have reported similar correlations between PTX3 plasma values and MACEs after DES-PCI. As shown in the study by Haibo et al.<sup>10</sup> PTX3 and cTnI plasma values after DES-PCI, multiple stents, and age, but not hsCRP levels, showed significantly independent association with major adverse cardiovascular events and PTX3 plasma values might be better inflammatory prognostic marker than CRP plasma values of MACEs in patients

suffering stable angina pectoris. According to Hudzik et al,<sup>9</sup> PTX3 plasma values show higher sensitivity to local inflammatory reaction than hsCRP in patients after BMS compared to DES implantation, and patients undergoing drug eluted implantation have been shown significantly decreased PTX3 plasma values than in those patients whom were deployed bare metal stent. Hudzik et al,<sup>9</sup> concluded that weaker inflammatory response and consequent lower PTX3 plasma values were due to anti-inflammatory effect of drug of DES-PCI. Therefore, patients undergoing DES-PCI reduced incidence of MACEs compared to BMS-PCI.<sup>22</sup> In the study by Kotooka et al,<sup>8</sup> any type of stent implantation provokes intense local immune reaction in damaged artery endothelium and increased PTX3 plasma values, causing wall thickening and developing restenosis after BMS-PCI. Pentraxin 3 plasma values determined at 24 hours after onset of myocardial infarction with ST-elevation are good prognostic factor of 1-month and 12-month mortality. Pentraxin 3 as a serum marker is good independent prognostic factor of left ventricle malfunction or a 12-month mortality.<sup>16</sup>

In our study, along with PTX3, cTnI plasma values have shown independent association with MACEs in STEMI patients after BMS-PCI. This finding was consistent with previous studies<sup>23</sup> reporting an independent association of higher cTnI plasma values with clinical outcomes after primary PCI for STEMI in short period of follow-up. Based on these results, cTnI plasma values are used for risk stratification of STEMI patients. Pentraxin 3 and cTnI, multiple stents and age were independent prognostic factors of MACEs in those patients suffering of stable angina pectoris after drug eluted stent implantation.<sup>10</sup> Higher cTnI plasma values were found as a good predictor of MACEs after non-urgent PCI.<sup>24,25</sup>

**Study limitations.** Although this study had prospective design, it included relatively small number of patients, and it has been carried out only in one research center. A larger number of patients undergoing BMS-PCI are necessary to support our PTX3 findings. Lastly, although we have determined PTX3, IL-6, IL-10, hsCRP, and cTnI plasma values before and 24 hours after BMS-PCI, more measurements of these markers should be carried out during follow-up period for better estimating risks of MACEs,

In conclusion, PTX3 might be better serum prognostic marker than IL-6, IL-10 or hsCRP for MACEs after BMS-PCI. It might help make better risk stratification of those patients who are undergoing BMS-PCI.

## References

1. Kunes P, Holubcova Z, Kolackova M, Krejssek J. Pentraxin 3 (PTX 3): an endogenous modulator of the inflammatory response. *Mediators Inflamm* 2012; 2012: 10.
2. Momiyama Y, Kawaguchi A, Kajiwara I, Ohmori R, Okada K, Saito I, et al. Prognostic value of plasma high-sensitivity c-reactive protein levels in Japanese patients with stable coronary artery disease: the Japan NCVC-collaborative inflammation cohort (JNIC) Study. *Atherosclerosis* 2009; 207: 272-276.
3. Jenny NS, Arnold AM, Kuller LH, Tracy RP, Psaty BM. Associations of pentraxin 3 with cardiovascular disease and all-cause death: The cardiovascular health study. *Arterioscler Thromb Vasc Biol* 2009; 29: 594-599.
4. Latini R, Maggioni AP, Peri G, Gonzini L, Lucci D, Mocarelli P, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. *Circulation* 2004; 110: 2349-2354.
5. Inoue T, Kato T, Uchida T, Sakuma M, Nakajima A, Shibazaki M, et al. Local release of c-reactive protein from vulnerable plaque or coronary arterial wall injured by stenting. *J Am Coll Cardiol* 2005; 46: 239-245.
6. Gottsauner-Wolf M, Zasmata G, Hornykewycz S, Nikfardjam M, Stepan E, Wexberg P, et al. Plasma levels of c-reactive protein after coronary stent implantation. *Eur Heart J* 2000; 21: 1152-1158.
7. Munk PS, Breland UM, Aukrust P, Skadberg O, Ueland T, Larsen AI. Inflammatory response to percutaneous coronary intervention in stable coronary artery disease. *J Thromb Thrombolysis* 2011; 31: 92-98.
8. Kotooka N, Inoue T, Fujimatsu D, Morooka T, Hashimoto S, Hikichi Y, et al. Pentraxin3 is a novel marker for stent-induced inflammation and neointimal thickening. *Atherosclerosis* 2008; 197: 368-374.
9. Hudzik B, Szkodzinski J, Pietka-Rzycka A, Danikiewicz A, Wojnar R, Lekston A, et al. Plasma pentraxin 3 may be a more sensitive marker of inflammatory response than high-sensitivity C-reactive protein after bare metal stent compared to drug-eluting stent implantation. *J Interferon Cytokine Res* 2013; 33: 280-284.
10. Haibo L, Xiaofang G, Chunming W, Jie Y, Guozhong C, Limei Z, et al. Prognostic value of Plasma pentraxin 3 level in patients with stable coronary artery disease after drug-eluted stent implantation. *Mediators Inflamm* 2014; 2014: 963096.
11. Chen SL, Liu Y, Lin L, Ye F, Zhang JJ, Tian NL, et al. Interleukin-6, but not C-reactive protein, predicts the occurrence of cardiovascular events after drug-eluting stent for unstable angina. *J Interv Cardiol* 2014; 27: 142-154.
12. Groot HE, Al Ali L, van der Horst ICC, Schurer RAJ, van der Werf HW, Lipsic E, et al. Plasma interleukin 6 levels are associated with cardiac function after ST-elevation myocardial infarction. *Clin Res Cardiol* 2019; 108: 612-621.
13. Hwang SJ, Park KW, Kwon DA, Kang HJ, Koo BK, Chae IH, et al. High plasma interleukin-6 is associated with drug-eluting stent thrombosis: possible role of inflammatory cytokines in the development of stent thrombosis from the Korea Stent Thrombosis Registry. *Circ J* 2011; 75: 1350-1357.
14. Monraats PS, Kurreeman FA, Pons Det al. Interleukin 10: a new risk marker for the development of restenosis after percutaneous coronary intervention. *Genes Immun* 2007; 8: 44-50.
15. Monraats PS, Kurreeman FA, Pons D, Sewgobind VD, de Vries FR, Zwinderman AH, et al. Plasma levels of interleukin 18, interleukin 10, and matrix metalloproteinase-9 and -137G/C polymorphism of interleukin 18 are associated with incidence of in-stent restenosis after percutaneous coronary intervention. *Genes Immun* 2013; 36: 1129-1135.
16. Tomandlova M, Jarkovskyy J, Tomandl J, Kubkova L, Kala P, Littnerova S, et al. Prognostic value of pentraxin-3 level in patients with STEMI and its relationship with heart failure and markers of oxidative stress. *Dis Markers* 2015; 2015: 1-11.
17. Akgul O, Baycan OF, Bulut U, Somuncu MU, Pusuroglu H, Ozyilmaz S, Gul M, et al. Long-term prognostic value of elevated pentraxin 3 in patients undergoing primary angioplasty for ST-elevation myocardial infarction. *Coron Artery Dis* 2015; 26: 592-597.
18. Latini R, Maggioni AP, Peri G, Gonzini L, Lucci D, Mocarelli P, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. *Circulation* 2004; 110: 2349-2354.
19. Helseth R, Solheim S, Opstad T, Hoffmann P, Arnesen H, Seljeflot I. The time profile of Pentraxin 3 in patients with acute ST-elevation myocardial infarction and stable angina pectoris undergoing percutaneous coronary intervention. *Mediators Inflamm* 2014; 2014: 608414.
20. Guo R, Li Y, Wen J, Li W, Xu Y. Elevated plasma level of pentraxin-3 predicts in-hospital and 30-day clinical outcomes in patients with non-ST segment elevation myocardial infarction who have undergone percutaneous coronary intervention. *Cardiology* 2014; 129: 178-188.
21. Matsui S, Ishii J, Kitagawa F, Kuno A, Hattori K, Ishikawa M, et al. Pentraxin 3 in unstable angina and non-ST-segment elevation myocardial infarction. *Atherosclerosis* 2010; 210: 220-225.
22. Palmerini T, Biondi-Zoccai G, Della Riva D, Stettler C, Sangiorgi D, D'Ascenzo F, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; 379: 1393-1402.
23. Hall TS, Hallén J, Krucoff MW, Roe MT, Brennan DM, Agewall S, et al. Cardiac troponin I for prediction of clinical outcomes and cardiac function through 3-month follow-up after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am Heart J* 2015; 169: 257-265.
24. Feldman DN, Kim L, Rene AG, Minutello RM, Bergman G, Wong SC. Prognostic value of cardiac troponin-I or troponin-T elevation following nonemergent percutaneous coronary intervention: a meta-analysis. *Catheter Cardiovasc Interv* 2011; 77: 1020-1030.
25. Feldman DN, Minutello RM, Bergman G, Moussa I, Wong SC. Relation of troponin I levels following nonemergent percutaneous coronary intervention to short- and long-term outcomes. *Am J Cardiol* 2009; 104 : 1210-1215.