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

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 ≥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.

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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. 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. It has been reported that increased PTX3 plasma value is a good prognostic serum marker for coronary artery disease. 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). Over the past years, several research studies have reported that PTX3 plasma value is increased after myocardial revascularization carried out by PCI, and it is associated with MACEs. 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.

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. 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. 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. 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. There is an association between plasma values of LI-10, MMP, IL-18 and the incidence of in-stent restenosis in patients who underwent PCI.

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 -80ºC 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±5.7 years). As shown in Figures 1 and 2, to all patients was deployed only one stent, and means of length (23±1.4 versus vs 21±1.9 mm: \( p>0.05 \)) and diameter of stent (3.1±0.2 vs 3.2±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 them with the values determined before BMS-PCI (4.96±0.78 vs 3.41±0.55 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±0.63 vs 6.78±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±0.37 vs 6.59±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±0.31 vs 7.81±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±0.82 vs 20.73±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±0.52 vs 20.56±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±0.39 vs 19.63±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±0.46 vs 4.08±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±0.77 vs 3.39±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 ≥5.042 ng/mL had increased cTnI plasma value (23.72±0.62 vs 19.26±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 ≥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

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### 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 | 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≥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., 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 (0.817-1.269) | 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            |
| Pentraxin-3     | r                | p               |                 |                 |
| 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
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Although this study had

marker than CRP plasma values of MACEs in patients

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prognostic value. These

correlations of PTX3 which is more specific for the

correlation with IL-6 and negative correlation with
Pentraxin-3 has shown strong and significant positive

adverse events using multivariate Cox regression test.
Pentraxin-3 plasma values increased at admission in hospital

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. In patients with STEMI, PTX3, but not CRP,

BNP, CK plasma values is good predictor of 3-month

mortality. 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. 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. Similar results

have been found in patients with non-ST-segment

elevation myocardial infarction.

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.

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,
cTnl, 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, PTX3 showed weak

correlation with hsCRP and cTnl 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., PTX3 and cTnl 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., 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. 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. In the

study by Kotooka et al. any type of stent implantation

provokes intense local immune reaction in damaged

daery 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

malfuction or a 12-month mortality.

In our study, along with PTX3, cTnl plasma values

have shown independent association with MACEs in

STEMI patients after BMS-PCI. This finding was consistent with previous studies reporting an

independent association of higher cTnl plasma values

with clinical outcomes after primary PCI for STEMI in

short period of follow-up. Based on these results, cTnl

plasma values are used for risk stratification of STEMI

patients. Pentraxin 3 and cTnl, multiple stents and

age were independent prognostic factors of MACEs in

those patients suffering of stable angina pectoris after
drug eluted stent implantation. Higher cTnl plasma

values were found as a good predictor of MACEs after

non-urgent PCI.

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 cTnl 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.
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