In this study, we evaluated the role of soluble thrombomodulin (sTM) to predict the development of MACE after PCI and stent placement.

**ABSTRACT**

Prediction of major adverse cardiac events (MACE) has recently been a focus of biomedical researches. Identification of the predictors can be useful to select at-risk patients for preventive treatment and healthy-life maintenance. The aim of this study was to evaluate the role of soluble thrombomodulin (sTM) to predict the development of MACE after PCI and stent placement. A total of 140 patients (aged 40-70 Years) undergoing percutaneous coronary intervention (PCI) and stent placement who’s had inclusion criteria were enrolled. Personal information and medical history were recorded in a form. Blood samples were collected 24 hours after PCI and serum level of sTM was measured. Patients were followed up for 18 months. Coronary angiography was done for patients with chest pain or positive results of non-invasive tests. End point of the study was MACE including death, MI, early or late stent Thrombosis, Target vessel revascularization (TVR) and target lesion revascularization (TLR). mean age of patients was 55.61 and most of them were male (65%)—most common risk factor was dislipidemia (46%) and LAD was most common vessel (69%)—in follow up time coronary angiography was done for 39 patients That 29 of Them (20.7) had MACE 13 target, Lesion restenosis, 10 target vessel restenosis, 2 MI and 3 Thrombosis and one patient dead. There was signification association between, Reference vessels diameter with MACE (2.56 ± 0.25 VS 3.28 ± 0.39 mm P < 0/001). Mean Blood level of sTM in patients who had MACE was lower than mean sTM in other patient but there was not statistically significant (13.99 ±2.65 VS 15.11 ±3.25 ng/ml P=0.070). But among patients who had not current risk factors, mean blood level of sTM in cases with MACE was significantly lower than mean of sTM in cases without MACE.(11.84 ± 1.92 VS 16.46 ± 3.38 ng/ml P= 0.019 ) but only 4 patients were in first group (patients without current risk factors who had MACE). Despite the result of our study indicate that in patients who had not current risk. Factors, development of MACE after PCI and stent placement associate with low blood level of sTM but introduce of sTM as a predictor, need to supplementary investigations with more number of the patients.

**Keywords:** MACE, sTM, Restenosis, Thrombosis, PCI Complications

**INTRODUCTION**

Despite advanced techniques of stent placement which cause fewer vessel walls injury as well as introduction of drug-eluting stents which results in the least induction of immune response, stent restenosis and thrombosis are still the most common complications after PCI and stent placement [1-5]. Also, the results of a study determined that development of drug-eluting stents has Reduced The Target Lesion restenosis however The number of MACE did not decrease [6]. Therefore identification of markers as predictors of MACE can be useful to select at risk patients for aggressive preventive treatment. There are several markers representing endothelial activation including TM, Von willebrond factor and Tissue Plasminogen activator [6-8].

Thrombomodulin (CD 141 or BD -3) is a cell surface glycoprotein which originally identified on vascular endothelium as a natural anticoagulant. Major function of TM is thrombin receptor.
The binding of thrombin to TM significantly decreases the thrombin's effect in conversion of fibrinogen to fibrin and activation of coagulation factors V, Vш and platelet [9-10]. TM-Thrombin complex also catalyze the protein C activation 1000 times faster than free thrombin. Activated protein C proteolytically inactivates the coagulation cofactors Va, and Vша. Thereby inhibiting the amplification of the coagulation system [11].

In addition, TM plays an important role in suppressing inflammation independent of anticoagulant activity [12]. Thrombin is a direct mediator of inflammation, acting as a chemoattractant for neutrophils and monocytes and stimulating endothelial cells to express monocyte chemoattractant protein 1 (MCP-1) and other chemokines. Thrombin also induces endothelial cell expression of ICAM-1, VCAM-1, E-selectin and p-selectin as well as platelet activating factor [13].

TM regulates C3b inactivation by factor I [14]. The findings of different studies showed that TM decreases of neointimal hyperplasia and TM gen polymorphisms are associated with CAD, Thrombosis and MI and high level of sTM signified protection and lower risk of CAD and reduced level of TM may contribute, to vascular damage and thrombosis in septicemia and cancer [15-20].

Objectives
In the present study we aim to evaluate the measurement of sTM in patients' serum can be useful to predict development of MACE after PCI and stent placement.

MATERIALS AND METHODS

In a prospective study from Jan to Sep 2014, 140 patients (aged 40-70 years) who underwent PCI and stent placement in the Rajaie cardiovascular medical and research center, Tehran, Iran and didn’t have any of the following criteria were included:

A - Inflammatory or autoimmune disease.
B - History of CABG or PCI
C – History of angiography, surgery and cardiac events in the past 3 months.
D - History of fever or infection diseases 2 weeks before admission.

The personal information and medical history were recorded in a data collection form. Blood samples were collected 24 hours after PCI and serum of samples were frozen at -70 until analysis.

The level of thrombomodulin was measured in samples by ELISA (Enzyme-Linked Immuno Sorbent Assay) method with the R & D company kits. Patients were followed up at 1, 3, 9, 18 months after PCI and coronary angiography was done for cases who had chest pain or positive results of noninvasive tests. End point of the study was MACE including death, MI, Early and late stent thrombosis, target vessel revascularization (TVR) and target lesion revascularization (TLR).

Statistical methods
Fitness interval variables to normal distribution was assessed via one-sample Kolmogorov-Smirnov test. Data presented as mean ± standard deviation for interval and count (percent) for the categorical variables. Association between the incidence of MACE and sTM or patients characteristics were investigated by students t or Pearson chi-square tests. Statistical analysis was performed by using IBM SPSS statistics 19 windows (IBM INC, Armonk, NY, USA). P values \( \leq 0.05 \) were considered as statistical significant.

RESULTS

Baseline characteristics
140 patients (mean age = 55.61 ± 9.8) male / female 91/49 participated. dislipidemia was most risk factor (46%). The prevalence of hypertension and diabetes mellitus was 43% and 29%. Baseline characteristics of the patients are listed in table 1. Most Patients had SVD and LAD was most common vessel (69%). lesion characteristics and PCI results were shown in table 2. In the follow up time coronary angiography was done for 39 patients. 29 patients had MACE (13 Target lesion revascularization, 10 target vessel revascularization, 3 thrombosis, 2 MI and one Patient dead)

Association between MACE with reference vessels diameter
There was significant association between reference vessels diameter with development of MACE (2.56 ±0.25 VS 3.28 ±0.39 mm, P<0.001).
**Association between MACE with blood level of sTM**
The mean serum level of sTM in patients who had MACE was lower than mean sTM in patients who had not MACE but there was not statistically significant (13.99 ± 2.65 VS 15.11± 3.02ng/mL P=0.07).

Between 140 cases of this study 19 patients had not current risk factors. In this group mean blood level of sTM in the cases who had not MACE (n=15) was significantly higher than mean of sTM in patients who had MACE (n=4). (16.46 ± 3.38 VS 11.48 ± 1.92 ng/mL p=0.019) mean serum level of sTM in different groups were shown in table 3.

**DISCUSSION AND CONCLUSION**
Since TM discovery as a critical cofactor in the initiation of the protein C anticoagulant pathway, biochemical and structural investigation revealed that TM ,especially its lectin like domain has potent anti-inflammatory function independent of anticoagulant, activity [10-11].

And also results of several studies determined that TM gene polymorphisms associated with human diseases and TM plays a role in thrombosis, strok, arteriosclerosis and cancer [15,19]. Previous study by the authors showed that there is a significant association between the down regulation of sTM and atherosclerosis [21] blann and MC collum introduced TM and von will brand factor as predictors of MACE [22]. wong et al showed that the stent grafts which coated with recombinant human TM significantly inhibited neoointimal hyperplasia compared with uncoated grafts [16]. Results of our study determined that in patients who had not current risk factors, development of MACE after PCI and stent emplacement correlate with low Serum Level of sTM, but introduce of sTM as a predictor of MACE in the patients need to supplementary investigations with more cases.

**REFERENCES**