CLINICAL TRIAL REPORT

Proprotein Convertase Subtilisin/Kexin Type 9 and Systemic Inflammatory Biomarker Pentraxin 3 for Risk Stratification Among STEMI Patients Undergoing Primary PCI

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Background and Aim: The aim of prospective study was to determine the prognostic value of combined measures of plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) and pentraxin 3 (PTX3) according to the culprit-plaque morphology (plaque rupture versus plaque erosion) in relation to the in patients with acute ST-elevated myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention.

Methods: A total of 434 patients with STEMI aged ≥18 years who underwent pre-intervention OCT imaging of culprit lesions between March 2017 and March 2019 were enrolled. Finally, 235 patients who meet the inclusion criteria were enrolled and the cohort was divided into 3 groups according to PCSK9 and PTX3 levels: group A: PCSK9 < median and Pentraxin 3 (N = 72/30.6%); group B: PCSK9 ≥ median or Pentraxin 3≥ median (N = 91/38.7%); group C: PCSK9 ≥ median and Pentraxin 3≥ median (N = 72/30.6%). MACEs were defined as a composite of all-cause death, myocardial infarction (MI) recurrence, and ischemic stroke, revascularization and heart failure.

Outcomes: During a median follow-up of 2.01 years, 50 patients has occurred MACE. Two-year MACE was higher in group C (23/31.9%) than in group B (16/17.6%) and group A (11/15.3%) (p = 0.028). There was a correlation between PCSK9 and PTX3 (r = 0.302, p < 0.003). In multivariable analysis adjusted for age, gender, risk factors, and serum indexes, being in group C remained independently associated with an increased risk of MACE (hazard ratio [HR]: 2.90; p = 0.010), and group B tended to have higher MACE (HR: 1.76; p = 0.172) compared with group A. Among patients with plaque erosion by OCT, group C was independently associated with an increased risk of MACE (HR: 9.04; p = 0.048) after fully adjustment. However, the significant association was absence among patients with plaque rupture.

Conclusion and Relevance: This study demonstrated the usefulness of combined measures of PCSK9 and PTX3 to enhance risk stratification in patients with STEMI especially among patients with plaque erosion. Patients with elevation of both PCSK9 and PTX3 had a markedly increased risk of MACE.

Keywords: pentraxin-3, PCSK9, plaque morphology characteristics, optical coherence tomography, major adverse cardiovascular events, ST-segment elevation myocardial infarction

Introduction

Despite the advances in contemporary therapies, cardiovascular atherosclerotic disease remains the leading cause of morbidity and mortality worldwide.

Inflammation is a significant process in atherosclerosis, leading to plaque rupture and acute coronary syndrome. Pro-protein convertase subtilisin/kexin type 9 (PCSK9) directly or indirectly contribute to atherosclerosis.[1] It induces the expression of secretion of inflammatory cytokines, endothelial cell apoptosis, inhibition of platelet activation and chemoattractants, thereby increasing inflammatory cell adhesion, and inflammation at the atherosclerotic vascular wall.[2] Furthermore, PCSK9 levels are considered causal in the development of atherosclerotic cardiovascular disease (ASCVD).[3–5] Pentraxin-3 (PTX3), produced mainly by dendritic cells, macrophages, and endothelial cells in response to primary inflammatory stimuli1, was involved in the pathogenesis of atherosclerosis and influenced clinical outcomes.[6–8] Optical coherence tomography (OCT), a cross-sectional and high-resolution intravascular imaging technique, allows the acquisition of detailed in vivo images of coronary plaque morphology characteristics, including plaque rupture (PR) and plaque erosion (PE) which are responsible for the majority of acute coronary events.[9–11] PCSK9 inhibitor has been reported that it could reduce plaque lipid content and inflammatory index of lipid-core.[12–14] Furthermore, PTX3 was proved to be a useful inflammatory marker to reflect the vulnerability of the plaque.[15] However, the clinical significance and incremental prognostic value of PCSK9 and PTX3 in the context of coronary plaque morphology characteristics are presently unknown. The aim of prospective study was to determine the prognostic value of combined measures of PCSK9 and PTX3 according to the culprit-plaque morphology (plaque rupture versus plaque erosion) in relation to the in patients with acute ST-elevated myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention.

Methods
Study Population
The Optical Coherence Tomography Examination in Acute Myocardial Infarction registry (OCTAMI) consecutive enrolled 434 STEMI patients hospitalized from March 2017 to March 2019 at Peking Union Medical College Fuwai Hospital. Finally, 235 patients who meet the inclusion criteria were enrolled. In terms of the principles of Declaration of Helsinki, the protocol was conducted and was given permission by the Ethics Committee of Fuwai Hospital. Personal information of the enrolled patients were not given away by concealing them. Patients have provided written informed consent specific to the OCT study (clinical trials.gov: NCT03593928).

The exclusion criteria of conducting OCT examinations were contraindication to aspirin or ticagrelor cardiac shock, allergy to contrast media, serious liver dysfunction, severe renal and hepatic insufficiency and lesions with characteristics that raised the difficulty and risk of performing OCT including left main coronary artery diseases, chronic total occlusion and heavily calcified vessels. The definition of STEMI followed the established criteria published previously.[16] There were only 17 cases of calcified nodules. Therefore, we excluded the cases of nodular calcification in the study in order to avoid the bias.

Primary Stenting and Antiplatelet Therapy
Emergent coronary angiography and procedures of primary PCI were conducted through radial access routinely. Primary PCI (including stenting/balloon dilatation/thrombus aspiration) was conducted using the standard criteria. During period of periprocedural anticoagulant therapy, bivalirudin or heparin (100 IU/kg) was routinely administered. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the physicians and stents commercially available were used. According to Thrombolysis in Myocardial Infarction (TIMI) grading system, the blood flow of infarct-related artery was evaluated. The relevant devices and certain PCI techniques including stenting, balloon dilation, intra-aortic balloon pump distal protection device, excimer laser coronary angioplasty and thrombus aspiration were at the discretion by operators. Patients undergone primary PCI were moved in the coronary care unit subsequently. The dual antiplatelet therapy following primary PCI consisted of oral aspirin and a P2Y12 inhibitor for at least 12 months.

OCT Image Acquisition
The imagines of intravascular OCT were performed in accordance with the described methods previously.[8] In summary, OCT images of culprit lesions were obtained by a catheter (Dragonfly™; LightLab Imaging, Inc., Westford, MA, USA) and a frequency-domain OCT system (ILUMIEN OPTIS™; St. Jude Medical/Abbott, St. Paul, MN, USA).

Quantitative Analysis of OCT Image
Three independent observers (JN.L., RZ.C., ZX. S.) who blinded to the basic clinical characteristics and angiographic presentations performed the OCT image analysis by the

offline review workstation (Ilumien Optis, St Jude Medical). Since there existed disagreements and divergences of views among observers on the results of OCT, it is necessary to have further in-depth discussions of this issue and resolve them by consensus. Based on the established criteria,[17–20] thin-cap fibroatheroma, lipid-rich plaque, lipid arc, macrophage infiltration, calcification, micro-vessels, white thrombi plaque rupture, plaque erosions and cholesterol crystals were defined (Figure 1).

Laboratory Tests

Venous blood samples were collected into a tube containing ethylene diamine tetraacetate (EDTA) before PCI and were centrifuged at $2000 \times g$ for 15min at room temperature and the plasma was frozen for PTX3 and stored at $-80°C$ until analysis. ELISA tests were performed on the instrumental platform of MultiSkan MK3 (Thermo). We have conducted a more detailed protocol and deposited it as supplement data. Measurement of circulating PCSK9 levels Circulating levels of PCSK9 were measured using enzyme-linked immunosorbent assay (DY3888; R&D Systems, Catalog) according to the manufacturer's instructions and compared with purified human PCSK9 standards. Circulating levels of PTX3 were determined by enzyme-linked immunosorbent assay (ELISA; R&D systems, USA).

Measurements

The clinical demographics such as age, gender, history of disease (including chronic kidney disease, hypertension, diabetes mellitus and hyperlipidemia), smoking status, primary PCI procedures, and medical treatments, were obtained from the electronic records of hospital.

Endpoints and Follow-Up

The composite of myocardial infarction recurrence, all-cause mortality, cardiac death, ischemic stroke, heart failure and revascularization were defined as MACEs. Well-trained physicians conducted the follow-up via records of hospital discharge and clinical notes by cellphone and direct interviews. The protocol of follow-up has been approved from the Institutional Review Board of Chinese Academy of Medical Sciences Fuwai Hospital. Well-trained physicians
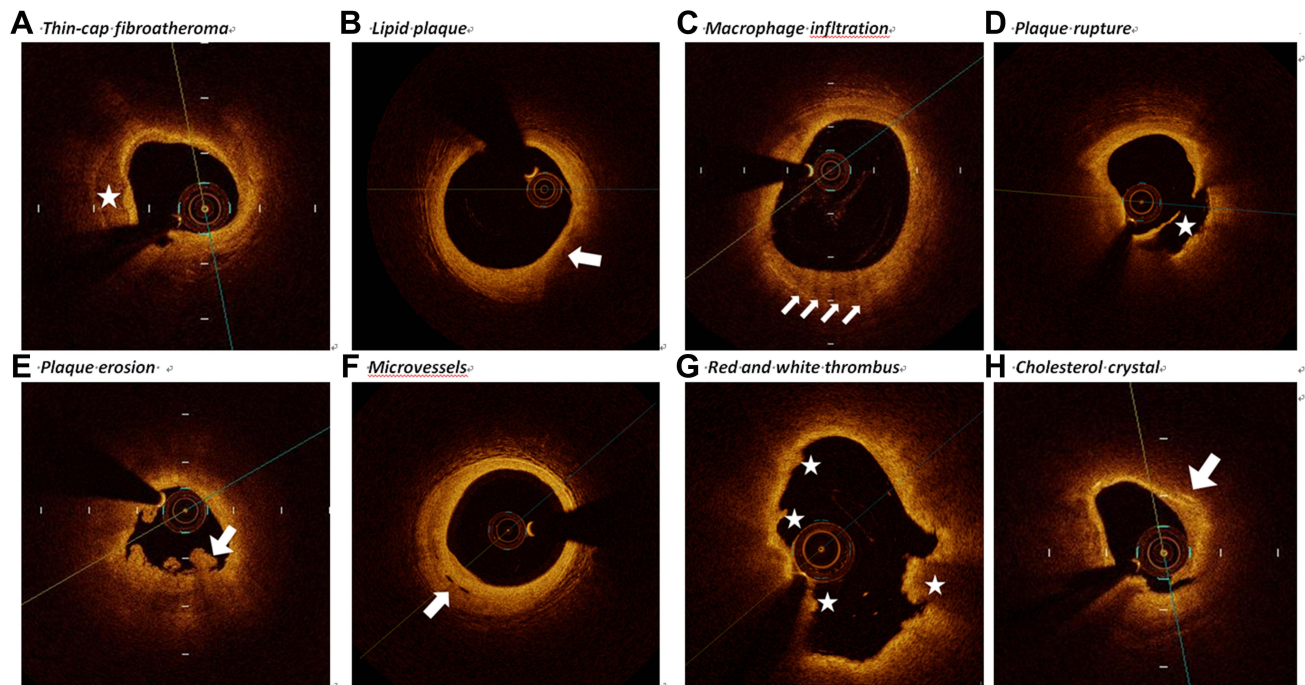

Figure 1 Representative cross-sectional optical coherence tomography images. (**A**) The identification of calcification was the presence of a well-delineated, low-back scattering region (asterisk). (**B**) Lipid plaque appears as signal-poor and diffusely bordered regions where overlying signal-rich bands (arrow). (**C**) Macrophages infiltration was defined as a distinct or confluent punctuate, signal-rich region of higher intensity than background speckle noise which creates conspicuous backward shadowing (arrows). (**D**) Plaque rupture (asterisk) was identified by uncompleted fibrous cap and cavity formation. (**E**) Plaque erosion identified by thrombus with an intact underlying plaque (arrows). (**F**) Microvessels was identified by the tubule luminal which without connection to the vessel lumen (arrow). (**G**) Red thrombus consists by red blood cells; relevant OCT images are characterized as high-back scattering protrusions with signal free shadowing (asterisk). White thrombi consisted by white blood cells and platelets. White thrombi were featured as low-back scattering, signal-rich and billowing projections protruding into the lumen (asterisk). (**H**) Cholesterol crystal (arrow) identified by backs cattering structures without prominent backward shadowing.

in charge of the follow-up endpoints, including all cause death, all-cause death, MI recurrence, revascularization, heart failure and ischemic stroke. They identified and extracted the primary endpoints from hospital records, medical records, emergency records, laboratory reports, and clinical notes which required to be sent to coronary disease centers. More than two professional physicians who were blinded to the clinical, angiographic and laboratory data confirmed the clinical endpoints.

Statistical Analysis

The continuous variables and categorical data are presented as the median (25th and 75th percentiles) and numbers (percentages). Mann–Whitney U-test and independent sample t-test were used to analysis the difference of groups for non-normally and normally distributed data respectively among continuous data. Categorical data were compared by Pearson's chi-squared (χ^2) test or Fisher's exact test, as appropriate. In order to assess the correlation of PCSK9 and PTX3 index with plaque morphology characteristics, multivariable cox regression with adjustments for confounding variables were conducted. Kaplan–Meier survival curves were performed to assess the incidence rate of MACEs and Log rank test was used to compare the discrepancy rates of cumulative events. Adjustments for confounding factors were made for variables including sex, gender, status of smoking, ejection fraction, hypertension, diabetes mellitus, hyperlipidemia, creatine kinase, heart rate, C-reactive protein, low-density lipoprotein and lipase activator. The areas under the receiver operating characteristic curve (ROC), sensitivity, specificity, Youden index and 95% confidence interval (CI) were calculated to evaluate the predictive ability of PCSK9 combined with PTX3 for MACEs.

Statistical significance was set at $P < 0.05$, and all p values were from a 2-sided test. Statistical analysis was performed using R Programming Language X64 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), SPSS (version 20.0; IBM Corp., Armonk, NY, USA) software and MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium).

Results
Comparison of Baseline Characteristics According to PCSK9 and PTX3 Level
A total of 235 patients who met the inclusion criteria were enrolled. A flow diagram illustrating the study sample selection process is shown in Figure 2. Table 1 describes the baseline clinical and biochemical characteristics of 235 participants stratified according to achieved PCSK9 levels and PTX3 at baseline (group A: PCSK9 <median and Pentraxin 3; group B: PCSK9 ≥ median or Pentraxin 3≥ median; group C: PCSK9 ≥ median and Pentraxin 3≥ median). Among the 235 patients included in this study (mean age: IQR 58 (50, 67) years; 80.9% men), 146 (62.1%) had hypertension and 70 (29.8%) had diabetes. Eighty-seven percent of patients were hyperlipidemia, 138 (58.7%) were in the status of current smoking, and 20 (8.5%) had a history of PCI. Incidence of MACE was 21.3%, mortality was 1.7%, MI recurrence was 3.8% and ischemic stroke was 3.8%. Thirty-two patients (13.6%) underwent revascularization after discharge and 1.7% experience heart failure. There were 72 patients (30.6%) in group A, 91 patients (38.7%) in group B, and 71 patients (30.6%) in group C. Patients in group C were lower prevalence of current smoking (p = 0.003) and the incidence of MACE (p = 0.028) and revascularization (p = 0.012) were more frequently compared with those in the 2 other groups (Table 1).

In order to prove the prognostic of PCSK9 value alone, we conducted the ROC for predicting MACEs to evaluate the diagnostic value of PCSK9 after fully adjustment (including gender, age, ejective fraction, basic syntax score, residual syntax score, hypertension, hyperlipidemia, diabetes mellitus, history of myocardial infarction, history of PCI, height, weight, heart rate, systolic blood pressure, diastolic blood pressure, killip classification, the use of aspirin and statin, baseline and peak level of TnI, baseline and peak level of BNP, hs-CRP, white blood cell, hemoglobin, platelet, creatinine, fasting glucose, hemoglobin A1c, total cholesterol, triglyceride, low-lipid protein and TyG index). The area under the ROC curve of PCSK9 was 0.887 (95% CI, 0.829–0.931). The Specificity is 92.91% and the Sensitivity is 69.44%. The results indicated that inflammatory biomarkers of PCSK9 could predict MACE with prognostic value (Supplement Figure 1). Correlation between LDL-chol and PCSK9 values among patients with primary PCI was conducted in Supplement Table 1. The results showed that there are no correlations between the LDL-chol and PCSK9 values among our cohort (p = 0.806).

Relationship Between PCSK9 and PTX3 and Characteristics of Plaque
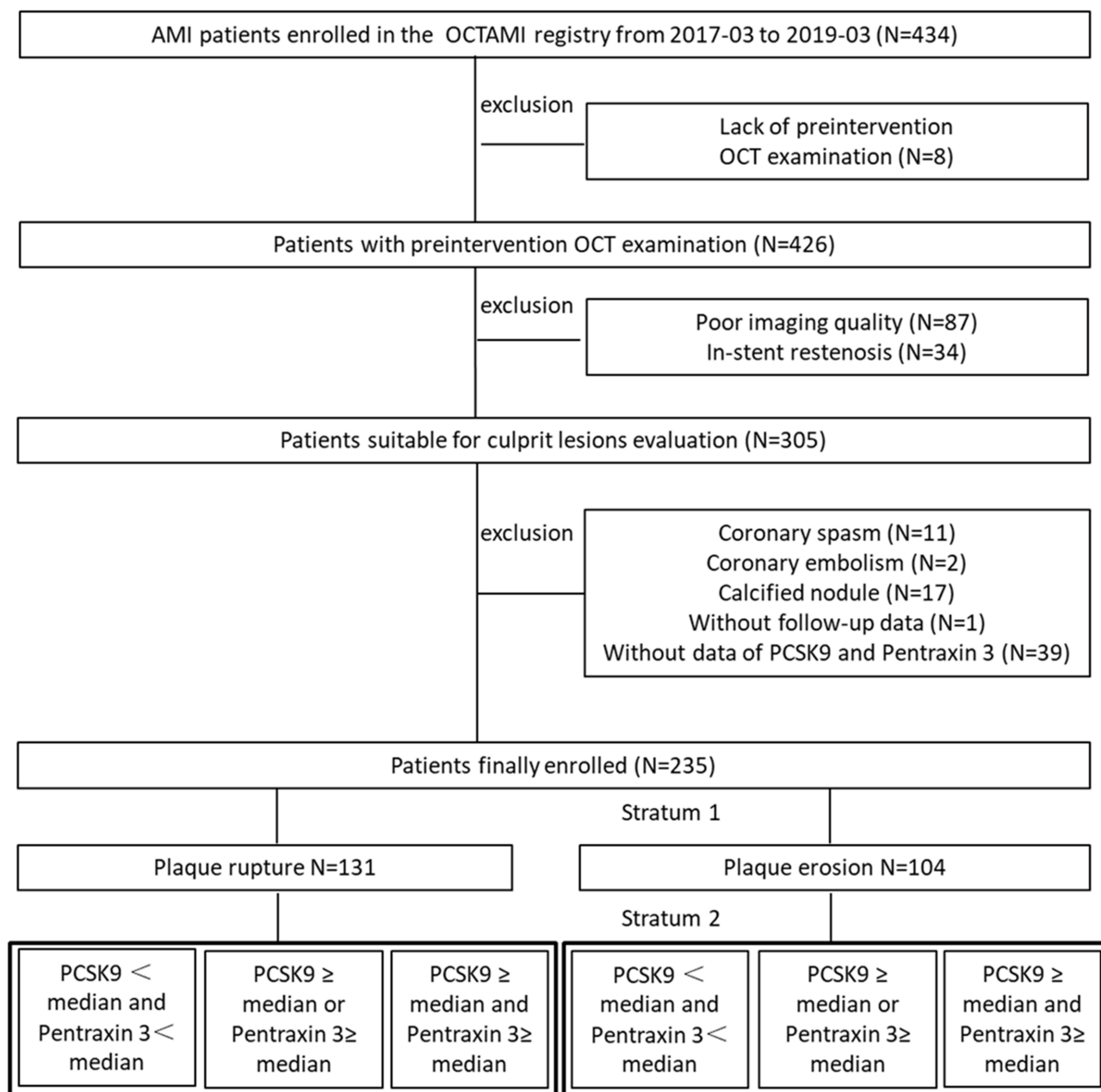There was a correlation between PCSK9 and PTX3 (r = 0.302, p < 0.003) (Figure 3). The proportion of patients

Figure 2 Flow chart.
Abbreviations: OCTAMI, Optical Coherence Tomography Examination in Acute Myocardial Infarction; OCT, optical coherence tomography; AMI, acute myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3.

with PTX3 level ≥median was 61.02% in the subset of patients with PCSK9 ≥median and 38.46% in the subset with a PCSK9 <median. PCSK9 correlated with characteristics of plaque by OCT including calcification (p = 0.033), arc of calcification (p = 0.005), micro-calcification (p = 0.005) and cholesterol crystal (p = 0.047) (Table 2). Correlation between biomarkers reflecting myocardial damage and PCSK9 and PTX3 among enrolled patients has been shown in Table 3. Table 3 has indicated that peak

level of troponin was correlated with Circulation PCSK9 value (p = 0.0146). We divided the cohort by microstructural OCT features of culprit lesions (plaque rupture and plaque erosion). Circulation PCSK9 value was significantly associated with calcification arc (p = 0.014) and micro-calcification (p = 0.021) among patients with plaque rupture. Among patients with plaque erosion, PCSK9 was correlated with thrombus characteristics of culprit lesions. Furthermore, PTX3 correlated with parameters of healing

Table 1 Baseline Clinical and Procedure Characteristics of the Study Population Divided by PCSK9 and PTX3

Variables	Total (N=235)	PCSK9 <Median and Pentraxin 3<Median (N=72)	PCSK9 ≥ Median or Pentraxin 3≥ Median (N=91)	PCSK9 ≥ Median and Pentraxin 3≥ Median (N=72)	P value
Age (years)	58.0 (49.5, 67.0)	56 (77.8)	75 (82.4)	59 (81.9)	0.726
Male [%(n)]	190 (80.9)	59.5 (50.0, 69.0)	57.0 (49.0, 66.0)	58.0 (49.5, 63.5)	0.379
Height (cm)	169.39 ± 6.59	169.56 ± 6.92	169.44 ± 6.77	169.01 ± 5.87	0.919
Weight (kg)	75.16 ± 11.47	76.39 ± 12.33	73.81 ± 9.45	75.42 ± 13.09	0.449
Heart rate (beats per minute)	76.21 ± 13.43	76.31 ± 14.47	74.75 ± 12.76	78.35 ± 12.94	0.327
Ejective fraction	56.0 (52.0, 60.0)	56.0 (52.0, 60.0)	55.0 (52.0, 58.0)	56.0 (49.5, 59.2)	0.605
SBP (mmHg)	122.73 ± 19.42	123.79 ± 19.51	121.15 ± 20.52	123.75 ± 17.67	0.648
DBP(mmHg)	79.24 ± 12.55	80.66 ± 12.98	78.22 ± 12.32	78.88 ± 12.35	0.485
Syntax score of base	15.5 (10.8, 22.5)	15.5 (11.0, 21.6)	17.5 (10.0, 23.2)	15.0 (11.0, 21.1)	0.951
Residual syntax score	4.0 (0.0, 8.0)	2.0 (0.0, 9.0)	5.0 (1.0, 7.0)	4.0 (1.0, 9.0)	0.443
Risk factors					
Hypertension[%(n)]	146 (62.1)	48 (66.7)	58 (63.7)	40 (55.6)	0.358
Diabetes[%(n)]	70 (29.8)	23 (31.9)	27 (29.7)	20 (27.8)	0.861
Hyperlipidemia[%(n)]	204 (86.8)	63 (87.5)	77 (84.6)	64 (88.9)	0.710
Current Smoking[%(n)]	138 (58.7)	47 (65.3)	55 (60.4)	36 (50)	0.003*
Previous PCI[%(n)]	20 (8.5)	4 (5.6)	6 (6.6)	10 (13.9)	0.141
CKD[%(n)]	4 (1.7)	1 (1.4)	1 (1.1)	2 (2.8)	0.874
Laboratory examinations					
LDL-cholesterol (mmol/L)	2.7 ± 0.9	2.7 ± 0.8	2.8 ± 0.9	2.8 ± 0.9	0.875
HDL-cholesterol at (mmol/L)	1.1 (0.9, 1.2)	1.1 (0.9, 1.2)	1.0 (0.9, 1.2)	1.1 (1.0, 1.3)	0.301
Total cholesterol at (mmol/L)	4.3 (3.6, 4.9)	4.2 (3.6, 4.7)	4.3 (3.7, 5.0)	4.3 (3.6, 5.2)	0.517
Triglycerides (mmol/L)	1.4 (0.9, 2.0)	1.4 (0.9, 1.8)	1.4 (1.0, 2.1)	1.5 (0.9, 2.2)	0.150
hs-CRP (mg/L)	6.2 (2.7, 10.9)	4.9 (2.9, 10.0)	6.2 (2.6, 10.9)	7.3 (2.8, 11.6)	0.531
D-dimer (ug/mL)	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	0.2 (0.1, 0.3)	0.2 (0.1, 0.4)	0.504
TnI (ng/L)	0.9 (0.1, 5.2)	0.9 (0.1, 3.6)	0.8 (0.1, 3.7)	1.2 (0.1, 6.3)	0.805
CK-MB	51.5 (20.8, 135.2)	60.5 (19.0, 150.5)	50.5 (23.0, 131.8)	49.5 (19.5, 125.8)	0.799
Peak level of TnI (ng/L)	22.1 (10.3, 44.9)	25.7 (10.7, 48.0)	21.9 (10.2, 45.9)	17.8 (10.7, 34.9)	0.555
BNP (ng/L)	172.7 (56.4, 618.6)	204.2 (59.4, 749.4)	195.7 (54.0, 627.2)	134.4 (47.3, 466.1)	0.712
Peak level of BNP (ng/L)	1558.0 (617.5, 3146.0)	1616.0 (933.6, 3560.0)	1543.0 (589.0, 3132.0)	1523.0 (583.5, 2394.0)	0.413
WBC 10^9/L	9.6 (7.9, 11.5)	9.8 (8.4, 12.1)	9.3 (7.6, 11.2)	9.5 (8.0, 11.6)	0.254
Hemoglobin	148.0 (136.0, 156.5)	147.5 (139.0, 158.2)	149.0 (136.5, 157.5)	145.0 (134.8, 153.2)	0.529
Platelet	222.0 (191.5, 279.5)	217.5 (190.0, 269.2)	218.0 (184.0, 286.0)	234.0 (204.0, 292.2)	0.205
Crea (umol/L)	80.1 (68.6, 92.3)	78.9 (68.5, 91.3)	78.8 (69.0, 91.5)	82.0 (68.3, 93.2)	0.916
Fasting plasma glucose	7.5 (6.3, 9.9)	7.7 (6.7, 10.0)	7.6 (6.0, 9.9)	7.4 (6.3, 9.7)	0.225
ALC	6.0 (5.6, 7.3)	6.0 (5.6, 7.4)	6.2 (5.5, 7.2)	5.9 (5.7, 7.1)	0.937
TyG	9.1 ± 0.7	9.0 ± 0.7	9.2 ± 0.7	9.1 ± 0.8	0.384
Discharge medication regimen					
Aspirin[%(n)]	226 (96.2)	69 (95.8)	87 (95.6)	70 (97.2)	0.929
Ticagrelor[%(n)]	123 (52.3)	37 (51.4)	47 (51.6)	39 (54.2)	0.932
Clopidogrel[%(n)]	112 (47.7)	35 (48.6)	44 (48.4)	33 (45.8)	0.932
ACEI/ARB[%(n)]	173 (73.6)	56 (77.8)	61 (67)	56 (77.8)	0.191
Beta-Blockers[%(n)]	204 (86.8)	65 (90.3)	78 (85.7)	61 (84.7)	0.570
Statin[%(n)]	227 (96.6)	69 (95.8)	87 (95.6)	71 (98.6)	0.656
Proton pump inhibitor[%(n)]	93 (39.6)	27 (37.5)	33 (36.3)	33 (45.8)	0.422
Angiographic findings					
Culprit vessels					0.301
LAD	109 (46.4)	31 (43.1)	44 (48.4)	34 (47.2)	
LCX	21 (8.9)	4 (5.6)	12 (13.2)	5 (6.9)	
RCA	105 (44.7)	37 (51.4)	35 (38.5)	33 (45.8)	

(*Continued*)

Table 1 (Continued).

Variables	Total (N=235)	PCSK9 <Median and Pentraxin 3<Median (N=72)	PCSK9 ≥ Median or Pentraxin 3≥ Median (N=91)	PCSK9 ≥ Median and Pentraxin 3≥ Median (N=72)	*P* value
Coronary artery lesions					0.354
SVD	55 (23.4)	23 (31.9)	17 (18.7)	15 (20.8)	
DVD	84 (35.7)	22 (30.6)	35 (38.5)	27 (37.5)	
TVD	96 (40.9)	27 (37.5)	39 (42.9)	30 (41.7)	
Pre-TIMI flow					0.881
0	146 (62.1)	43 (59.7)	58 (63.7)	45 (62.5)	
1	12 (5.1)	5 (6.9)	4 (4.4)	3 (4.2)	
2	23 (9.8)	5 (6.9)	9 (9.9)	9 (12.5)	
3	54 (23.0)	19 (26.4)	20 (22)	15 (20.8)	
AHA classification					0.015
A	2 (0.9)	0 (0)	0 (0)	2 (2.8)	
B1	23 (9.8)	2 (2.8)	14 (15.4)	7 (9.9)	
B2	34 (14.5)	8 (11.1)	12 (13.2)	14 (19.7)	
C	175 (74.8)	62 (86.1)	65 (71.4)	48 (67.6)	
Endpoint events					
MACE [%(n)]	50 (21.3)	11 (15.3)	16 (17.6)	23 (31.9)	0.028*
Death [%(n)]	4 (1.7)	1 (1.4)	2 (2.2)	1 (1.4)	1.000
Recurrent MI [%(n)]	9 (3.8)	1 (1.4)	3 (3.3)	5 (6.9)	0.228
Stroke [%(n)]	9 (3.8)	4 (5.6)	3 (3.3)	2 (2.8)	0.763
Revascularization	32 (13.6)	7 (9.7)	8 (8.8)	17 (23.6)	0.012*
Heart failure [%(n)]	4 (1.7)	0 (0)	2 (2.2)	2 (2.8)	0.571

Notes: Continuous data are presented as median (25th, 75th percentiles). Categorical data are presented as number (%). *P<0.05.
Abbreviations: DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TnI, troponin; CK-MB, creatine kinase isoenzymes; LPA, lipse activator; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; hs-CRP, high sensitive C-reactive protein; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; AHA, American Heart Association; MACE, major adverse cardiovascular events; MI, myocardial infarction; TyG, triglyceride glucose; PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3.

plaque (p = 0.004) and minimal lumen area (p = 0.012) among all enrolled cohort. Among group of plaque erosion, PTX3 correlated with fibrous plaque (p = 0.009) and healing plaque (p = 0.010). However, PTX3 was significantly associated with minimal lumen area merely (p = 0.001) among patients with plaque rupture.

Outcomes According to PCSK9 and PTX3 Plasma Level

During a median follow-up of 2.01 years (interquartile range: 1.96 to 2.96 years), 50 patients occurred MACE. Kaplan–Meier curves were generated for the cumulative incidence of MACEs for up to a median of 2.01 years stratified by PCSK9 and PTX3 among the PR and PE subgroups. The 2-year MACE rate was higher (p = 0.0075) in group C (23/31.9%) than in group B (16/17.6%) and group A (11/15.3%) in all enrolled cohort (Figure 4A). Notably, among patients with plaque erosion, there were significant differences among the group with PCSK9 ≥ median and Pentraxin 3≥ median (p = 0.028)

(Figure 4B). However, the difference was not significant among the patients with plaque rupture (p = 0.170) (Figure 4C).

We tried to prove the prognostic function of combined PCSK9 and PTX3 values for cardiac events are as follows. Firstly, the prognostic value of PCSK9 combined with PTX3 is higher than PCSK9 values alone. We conducted the area under the receiver operating characteristic curve (ROC) for predicting MACEs to evaluate the diagnostic value of PCSK9 combined with PTX3 after fully adjustment (adjusted factors including gender, age, hypertension, hyperlipidemia, diabetes mellitus, the use of statin, hs-CRP, triglyceride, low-lipid protein). The area under the ROC curve of PCSK9 and PCSK9 combined with PTX3 after fully adjustment was 0.730 (95% CI, 0.650–0.770) and 0.732 (95% CI, 0.671–0.778). The results indicated that the combination of two inflammatory biomarkers could predict MACE with more prognostic value compared with PCSK9 or PTX3 values alone (Figure 5).
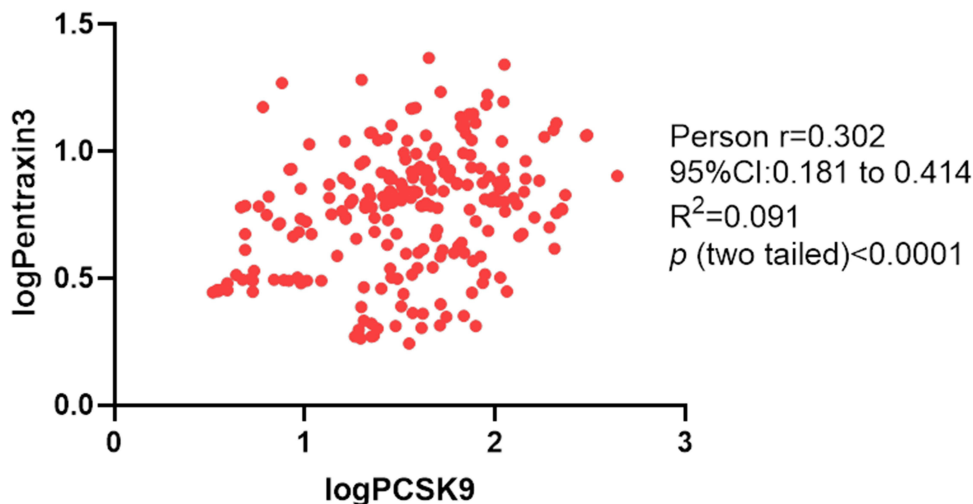
Correlation Between PCSK9 and Pentraxin3

Figure 3 Correlation between PCSK9 and pentraxin 3. Table 4 revealed the Impact of PCSK9 and PTX3 on endpoints among all enrolled cohort by univariable and Multivariable Analyses. Table 5 revealed the Impact of PCSK9 and PTX3 on Major adverse cardiovascular events among plaque rupture and plaque erosion cohort by univariable and Multivariable Analyses.

Notes: Data presented are HRs and 95% CI. Adjust I model adjusts for sex and age; Adjust II model adjusts for adjust I plus ejection fraction, smoke, hypertension, hyperlipidemia, diabetes mellitus; Adjust III model adjusts for adjust II + creatine kinase, heart rate, low-density lipoprotein; lipase activator and C-reactive protein. *P < 0.05.

Abbreviations: Adj., adjusted; MACE, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3; REF, reference.

Tables 4 and 5 show the crude and adjusted multi-variable relationships between MACEs stratified according to PCSK9 and PTX3 index with PR and PE among the subgroups (Tables 4 and 5, respectively). In univariable analysis, group C was associated with a 2.71-fold increase (p = 0.007) and group B with a 1.28-fold increase (p = 0.531) in MACEs compared with group A (Tables 4 and 5) among all enrolled cohort (p for trend = 0.005). After adjustments for several variables in different models, including sex, age, ejection fraction, smoke, hypertension, hyperlipidemia, diabetes mellitus, creatine kinase, heart rate, C-reactive protein, low-density lipoprotein and lipase activator, group C remained independently associated with increased risk of MACE (HR, 2.90; 95% CI, 1.29–6.25; P = 0.010), whereas there was a trend for an association between group B and increased MACE compared with group A (HR, 1.76; 95% CI, 0.78–3.94; P = 0.172) (p for trend=0.010) (Table 4). Notably, the effect of elevation of PCSK9 and PTX3 on MACEs was similar in the fully adjusted Cox regression models among patients with plaque erosion (HR: 9.04; 95% CI = 1.02 to 79.83; p = 0.048). However, the significant association was absent among patients with plaque rupture (Table 5).

Disscussion
Main Finding

To the best of our knowledge, the present study is the first study to explore the prognostic value of combined measures of PCSK9 and PTX3 according to the culprit-plaque morphology (PR versus PE) in relation to the in patients with STEMI who underwent primary PCI via OCT. The main findings of this study can be summarized as 8 follows: The main findings of the present study were as follows: 1) measurement of PCSK9 plasma levels provided incremental prognostic information beyond that obtained by PTX3; and 2) patients with elevation of both PCSK9 and PTX3 had a markedly increased risk of MACEs compared with those without elevation of these 2 biomarkers.

PCSK9 and PTX3 and Cardiovascular Risk

The previous study has tried to make the combination of PCSK9 and PTX3 among patients with severe sepsis or septic shock. However, the effects on the patients with acute coronary syndrome are remained unknown. In the sub-analysis of the ALBIOS trial, Vecchie[21] et al has investigated the correlations between levels of PCSK9 and PTX3 among patients with severe sepsis or septic

Table 2 Correlation Between Blood Biomarkers and OCT Characteristics Among Patients with Plaque Rupture or Plaque Erosion

Variables	Circulation PCSK9 value						PTX 3 value					
	All Enrolled		Plaque Rupture Cohort		Plaque Erosion Cohort		All Enrolled		Plaque Rupture Cohort		Plaque Erosion Cohort	
	R_1	P value	R_2	P value	R_3	P value	R_1'	P value	R_2'	P value	R_3'	P value
Lipid-rich plaque	−0.030	0.653	−0.071	0.418	−0.016	0.869	0.006	0.927	−0.014	0.870	0.029	0.771
Fibrous plaque	0.008	0.908	0.018	0.842	0.052	0.601	−0.119	0.070	−0.041	0.646	−0.253	0.009*
Mixed plaque	−0.095	0.146	−0.043	0.629	−0.152	0.125	0.079	0.225	−0.074	0.398	0.150	0.127
Healing plaque	−0.053	0.416	−0.073	0.406	−0.020	0.844	−0.185	0.004*	−0.126	0.151	−0.251	0.010*
Calcification	−0.139	0.033*	−0.136	0.120	−0.165	0.094	−0.085	0.194	−0.020	0.818	−0.143	0.147
Calcification arc	0.183	0.005*	0.214	0.014*	0.027	0.789	−0.123	0.060	−0.158	0.072	−0.057	0.565
Micro-calcification	−0.182	0.005*	−0.202	0.021*	−0.165	0.094	−0.075	0.254	−0.003	0.972	−0.143	0.147
Macrophage	0.021	0.754	0.103	0.242	−0.143	0.147	0.029	0.660	0.043	0.625	0.048	0.631
Micro-vessels	0.026	0.691	−0.026	0.764	0.116	0.241	−0.064	0.329	−0.114	0.194	−0.033	0.740
Cholesterol crystal	−0.130	0.047*	−0.154	0.079	−0.096	0.331	−0.104	0.113	−0.162	0.065	−0.052	0.603
Thrombus	−0.104	0.110	-	-	−0.206	0.036*	−0.007	0.915	-	-	−0.001	0.995
Minimal FCT	0.050	0.445	0.067	0.445	0.096	0.332	0.049	0.445	0.002	0.983	0.047	0.639
TCFA	−0.013	0.846	−0.038	0.663	0.009	0.926	0.168	0.010*	0.135	0.123	0.343	0.000*
Maximal lipid arc	−0.047	0.470	−0.106	0.226	−0.006	0.332	0.041	0.532	0.112	0.205	0.016	0.872
MLA	−0.070	0.288	−0.031	0.728	−0.165	0.094	0.163	0.012*	0.294	0.001*	0.052	0.603

Note: *$P < 0.05$.
Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3; TCFA, thin-cap fibroatheroma; FCT, fibrous cap thickness; MLA, minimal lumen area; R, relevant.

Table 3 Correlation Between Biomarkers Reflecting Myocardial Damage and PCSK9 and PTX3 Among Enrolled Patients

Variables	Circulation PCSK9 value				PTX 3 value			
	R	P value	95% CI Lower	95% CI Upper	R'	P 'value	95% CI Lower'	95% CI Upper'
Troponin at baseline	−0.0845	0.1968	−0.2102	0.0440	0.1001	0.1261	−0.0283	0.2252
Peak level of troponin	−0.1588	0.0148*	−0.2811	−0.0315	0.0742	0.2570	−0.0543	0.2003
CK-MB	−0.1055	0.1369	−0.2408	0.0337	0.0994	0.1613	−0.0399	0.2349
BNP at baseline	−0.0375	0.5669	−0.1647	0.0909	0.0469	0.4744	−0.0816	0.1738
Peak level of BNP	−0.0828	0.2058	−0.2086	0.0456	0.0329	0.6158	−0.0955	0.1602

Note: *$P < 0.05$.
Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3; CK-MB, creatine kinase isoenzymes; BNP, Brain Natriuretic Peptide; R, relevant.

shock with ranked Spearman's coefficients and found that PCSK9 correlated positively with PTX3 at the three time-points. They found that patients with septic shock presenting with lower plasma PCSK9 levels experienced higher mortality rate.[21] PTX3, an acute-phase reactant[22] belonging to the CRP family (pentraxins), has been evaluated as a biomarker of disease severity and outcomes.[23–25] Rannikko et al[26] have observed that there is a significant positive correlation between PCSK9 and CRP levels. The expression of PCSK9 is stimulated by mediators of inflammatory[27] and the elevated level of PCSK9 is correlated with remarkable systemic inflammation. The positive correlation between PCSK9 and PTX3 has been confirmed by previous study.[21]

PCSK9, through promoting lysosome degradation of hepatic low-density lipoprotein (LDL) receptor to decrease the clearance of plasma LDLs, is now identified as a major player in hypercholesterolaemia and atherosclerosis pathophysiology.[28] Besides the hepatocyte LDL-receptor, PCSK9 can regulate LDL-receptor in other cells, including macrophages, lymphocytes, vascular smooth muscle cells and endothelial cells.[29] PTX3, as a significant symbol of systemic inflammation, has been described to be associated with endothelial dysfunction in different cardiovascular disorders and correlated with increased risk of MACEs which widely established in previous studies in line with our results.[30,31] Marked as an innate immunity protein, large amounts of circulating PTX3 increase during
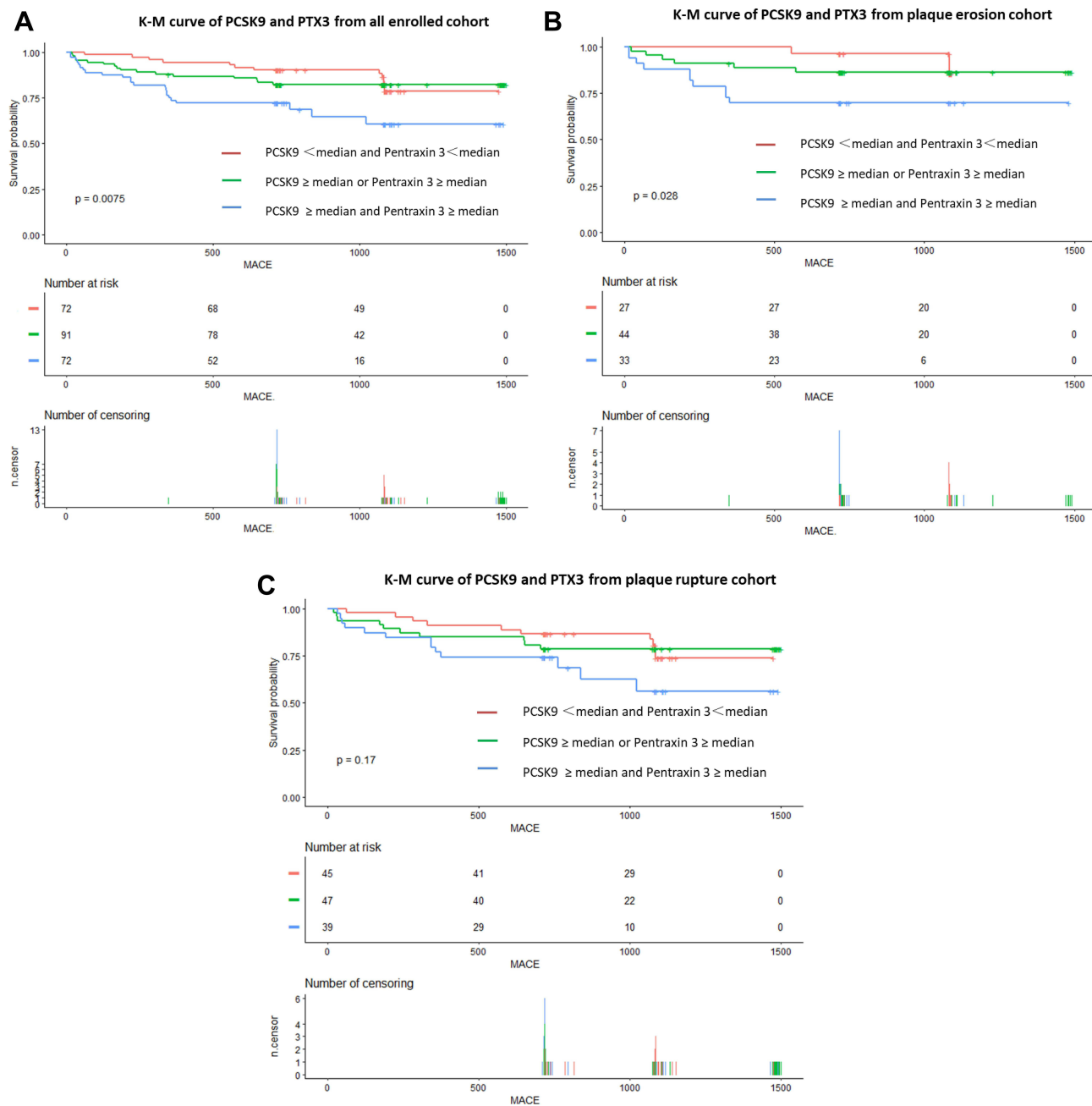
Figure 4 Kaplan–Meier Curves of MACE stratified by achieved PCSK9 and PTX3 in the setting of all enrolled cohort or plaque rupture/ plaque erosion. (**A**), Kaplan–Meier Curves of MACE stratified by achieved PCSK9 and PTX3 in the setting of all enrolled cohort. Test of trend: P = 0.00075. (**B**), Kaplan–Meier Curves of MACE stratified by achieved PCSK9 and PTX3 in the setting of patients with plaque erosion. Test of trend: P = 0.028. (**C**), Kaplan–Meier Curves of MACE stratified by achieved PCSK9 and PTX3 in the setting of patients with plaque rupture. Test of trend: P = 0.170.
Abbreviations: PCSK9, proprotein convertase subtilisin/kexin type; PTX3, pentraxin 3.

inflammation to affect the cardiovascular system.[32] The present study showed that patients with elevation of circulating PCSK9 and PTX3 has been exposure higher incidence of MACE compared with those with none or only 1 of these 2 biomarkers elevated. Furthermore, the association between elevation of these blood biomarkers and MCAEs

persisted after adjustment for these factors. The present study has showed that hsCRP values were higher in group B and C than in group A. The inflammatory index of hs-CRP represents a major biomarker of inflammation and associated risk in cardiovascular disease. The levels of hs-CRP identify groups of patients with higher risk of
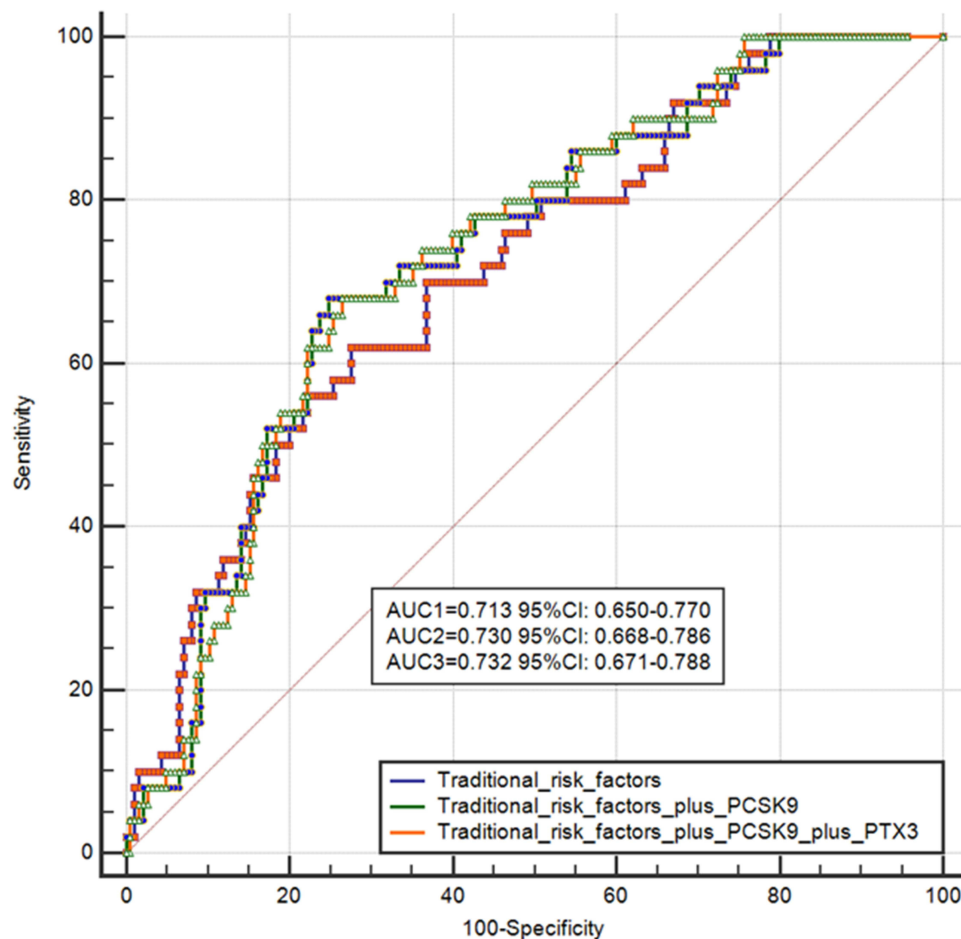
Figure 5 The prognostic value of PCSK9. We conducted the area under the receiver operating characteristic curve (ROC) for predicting MACEs to evaluate the diagnostic value of PCSK9 combined with PTX3 after fully adjustment (adjusted factors including gender, age, hypertension, hyperlipidemia, diabetes mellitus, the use of statin, hs-CRP, triglyceride, low-lipid protein). The area under the ROC curve of PCSK9 and PCSK9 combined with PTX3 after fully adjustment was 0.730 (95% CI, 0.650–0.770) and 0.732 (95% CI, 0.671–0.778).
Abbreviations: ROC, receiver operating characteristic curve; CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type; PTX3, pentraxin 3.

cardiovascular disease achieving better identify groups of prevention in response to PCSK9 inhibition. In the study of FOURIER, there was a stepwise risk increment by level of hs-CRP even in patients with extremely low levels of LDL-C.[33] The correlation of elevated CRP levels and cardiovascular disease has been well established. Furthermore, the effect of lacking of CRP-lowering does not bring doubts the clinical benefit of PCSK9 inhibitors which have been shown to reduce cardiovascular outcomes.[34,35] It would be of paramount significant to elucidate the role of PCSK9 beyond hs-CRP modulation and pathways connecting PCSK9 to vascular inflammation. There are evident to revealed that PCSK9 is expressed in atherosclerotic plaques[36] and small interfering RNA-mediated knockdown of PCSK9 in human macrophages has been found to reduce inhibitor of nuclear factor kappa B-α degradation, thereby

reducing the expression of pro-inflammatory genes.[37] In order to regulate related inflammation together with the complement system, the functions of CRP and PTX3 which are deeply involved in the pathogenesis of cardiovascular disease linked to inflammation are to coordinate spatially and temporally targeted clearance of injured tissue components.[38] It has been proved that circulating elevated CRP and PTX3 levels could provide prognostic information for a variety of clinical diagnosis of cardiovascular disease.[39]

In the present study, there was only a strong correlation between PCSK9 and PTX3, and these 2 biomarkers were complementary in terms of prognostication. Approximately one-half of the patients with PCSK9 level ≥median had elevation of PTX3. In contrast, approximately one-quarter of patients with PCSK9 <median had

Table 4 Univariable and Multivariable Analyses of the Impact of PCSK9 and PTX3 on Endpoints Among All Enrolled Cohort

Group	N.Events (%)	Crude Model		Adjust Model I		Adjust Model II		Adjust Model III	
		Crude HR(95% CI)	Crude P value	Adj I. HR(95% CI)	Adj. P value	Adj II. HR(95% CI)	Adj. P value	Adj III. HR(95% CI)	Adj. P value
MACE									
PCSK9 <median and Pentraxin 3<median	11 (15.3)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	16 (17.6)	1.28 (0.59–2.76)	0.531	1.42 (0.65–3.07)	0.376	1.55 (0.7–3.43)	0.280	1.76 (0.78–3.94)	0.172
PCSK9 ≥ median and Pentraxin 3≥ median	23 (31.9)	2.71 (1.31–5.58)	0.007*	2.93 (1.42–6.06)	0.004*	3.03 (1.37–6.68)	0.006*	2.90 (1.29–6.52)	0.010*
Trend test	50 (21.3)	1.7 (1.18–2.47)	0.005*	1.76 (1.22–2.53)	0.003*	1.76 (1.18–2.62)	0.006*	1.70 (1.14–2.54)	0.010*
All-cause mortality									
PCSK9 <median and Pentraxin 3<median	1 (1.4)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	2 (2.2)	1.51 (0.14–16.73)	0.735	1.93 (0.17–21.46)	0.591	3.65 (0.11–117.8)	0.466	33.66 (0.03–INF)	0.363
PCSK9 ≥ median and Pentraxin 3≥ median	1 (1.4)	1.00 (0.06–15.99)	0.999	1.21 (0.07–19.41)	0.895	5.69 (0.11–284.93)	0.384	13.40 (0.03–INF)	0.430
Trend test	4 (1.7)	1.00 (0.28–3.54)	0.999	1.10 (0.32–3.77)	0.880	2.26 (0.37–13.94)	0.378	2.45 (0.34–17.78)	0.380
Recurrent MI									
PCSK9 <median and Pentraxin 3<median	1 (1.4)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	3 (3.3)	2.55 (0.26–24.56)	0.418	2.84 (0.29–27.42)	0.368	3.28 (0.33–32.36)	0.309	2.88 (0.28–30.02)	0.378
PCSK9 ≥ median and Pentraxin 3≥ median	5 (6.9)	5.65 (0.65–48.69)	0.115	6.74 (0.78–58.57)	0.084	8.83 (0.92–84.46)	0.059	8.36 (0.83–84.31)	0.072
Trend test	9 (3.8)	2.33 (0.90–5.99)	0.080	2.53 (0.98–6.52)	0.055	2.90 (1.04–8.04)	0.041*	2.90 (1.00–8.40)	0.05
Revascularization									
PCSK9 <median and Pentraxin 3<median	7 (9.7)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	8 (8.8)	0.97 (0.35–2.68)	0.953	1.03 (0.37–2.85)	0.956	1.17 (0.42–3.27)	0.766	1.1 (0.38–3.20)	0.863
PCSK9 ≥ median and Pentraxin 3≥ median	17 (23.6)	3.02 (1.24–7.33)	0.015*	3.18 (1.31–7.74)	0.011*	3.39 (1.30–8.89)	0.013*	3.09 (1.14–8.43)	0.027*
Trend test	32 (13.6)	1.91 (1.19–3.07)	0.008*	1.95 (1.21–3.12)	0.006*	1.93 (1.16–3.22)	0.011*	1.85 (1.09–3.13)	0.023*
Ischemic stroke									
PCSK9 <median and Pentraxin 3<median	4 (5.6)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	3 (3.3)	0.65 (0.14–2.9)	0.569	0.73 (0.16–3.31)	0.681	0.79 (0.17–3.7)	0.767	1.06 (0.21–5.22)	0.946
PCSK9 ≥ median and Pentraxin 3≥ median	2 (2.8)	0.58 (0.10–3.2)	0.531	0.64 (0.11–3.53)	0.606	0.86 (0.15–5.05)	0.865	0.95 (0.15–6.04)	0.955
Trend test	9 (3.8)	0.74 (0.31–1.76)	0.503	0.79 (0.34–1.85)	0.587	0.91 (0.37–2.21)	0.830	0.98 (0.40–2.42)	0.970

Table 5 Univariable and Multivariable Analyses of the Impact of PCSK9 and PTX3 on Major Adverse Cardiovascular Events Among Plaque Rupture and Plaque Erosion Cohort

Group	Crude Model			Adjust Model I		Adjust Model II		Adjust Model III	
	N.Events(%)	Crude HR(95% CI)	Crude P value	Adj I. HR(95% CI)	Adj. P value	Adj II. HR(95% CI)	Adj. P value	Adj III. HR(95% CI)	Adj. P value
Plaque rupture									
MACE									
PCSK9 <median and Pentraxin 3<median	9 (20)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	10 (21.3)	1.19 (0.48–2.92)	0.711	1.25 (0.50–3.1)	0.629	1.26 (0.48–3.33)	0.635	1.4 (0.52–3.79)	0.506
PCSK9 ≥ median and Pentraxin 3≥ median	13 (33.3)	2.10 (0.89–4.95)	0.089	2.17 (0.92–5.11)	0.075	2.25 (0.84–5.98)	0.106	2.4 (0.87–6.57)	0.090
Trend test	32 (24.4)	1.47 (0.95–2.28)	0.087	1.49 (0.96–2.31)	0.073	1.50 (0.91–2.47)	0.116	1.54 (0.93–2.57)	0.096
Plaque erosion									
MACE									
PCSK9 <median and Pentraxin 3<median	2 (7.4)	REF	REF	REF	REF	REF	REF	REF	REF
PCSK9 ≥ median or Pentraxin 3≥ median	6 (13.6)	1.97 (0.40–9.77)	0.406	2.07 (0.42–10.35)	0.374	2.42 (0.46–12.81)	0.299	8.57 (1.02–71.77)	0.048*
PCSK9 ≥ median and Pentraxin 3≥ median	10 (30.3)	5.12 (1.12–23.46)	0.035*	5.51 (1.16–26.1)	0.032*	3.88 (0.76–19.7)	0.102	9.04 (1.02–79.83)	0.048*
Trend test	18 (17.3)	2.37 (1.18–4.75)	0.015*	2.44 (1.20–4.99)	0.014*	1.89 (0.90–3.98)	0.093	2.45 (0.92–6.51)	0.073

Notes: Table 4 revealed the Impact of PCSK9 and PTX3 on endpoints among all enrolled cohort by univariable and Multivariable Analyses. Table 5 revealed the Impact of PCSK9 and PTX3 on Major adverse cardiovascular events among plaque rupture and plaque erosion cohort by univariable and Multivariable Analyses. Data presented are HRs and 95% CI. Adjust I model adjusts for sex and age; Adjust II model adjusts for adjust I plus ejection fraction, smoke, hypertension, hyperlipidemia, diabetes mellitus; Adjust III model adjusts for adjust II + creatine kinase, heart rate, low-density lipoprotein; lipase activator and C-reactive protein. *P < 0.05.
Abbreviations: Adj., adjusted; MACE, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin type 9; PTX3, pentraxin 3; REF, reference.

PTX3 level ≥median. These findings might be explained by the fact that PCSK9 and PTX3 are activated by different mechanisms in response to various pathophysiological pathways and/or stimuli. There is accumulating evidence indicating that PCSK9 could increase vascular inflammation locally and contribute to atherosclerotic plaque progression among hyper-cholesterolaemia cohort.[40] Among several previously published epidemiological studies, the connection between PCSK9 and key inflammation markers (including white blood cells, fibrinogen, and hs-CRP) has been investigated.[41] In a single-centre study of CAD patients who were not on lipid-lowering therapy in China, plasma levels of PCSK9 were positively and independently associated with white blood cell count subsets, lymphocyte count and neutrophil count.[42] A cross-sectional study has verified that the circulating levels of PCSK9 were positively associated with those of fibrinogen among stable CAD and the interaction was suggested to be one of the underlying mechanisms involved in the progression of atherosclerosis.[43]

PCSK9 and PTX3 and Plaque Morphology Characteristics by OCT

The most striking finding in the current study was the prognostic role of the PCSK9 combined with PTX3 among patients with plaque rupture or plaque erosion. After adjustment for confounding factors, the incidence of MACEs was significantly higher among participants in the group with PCSK9 ≥ median and Pentraxin 3≥ median in the presence of PE. However, this tendency was absent in patients with PE. Rupture and erosion of the coronary culprit plaques are the primary cause of acute coronary disease.[44] Previous studies comparing the influence of PE and PR in acute MI demonstrated that despite similar clinical characteristics, patients with PE tended to present high-risk clinical characteristics, more complex angiographic features and high-risk plaque features, such as larger infarct sizes,[45] more multi-vessel lesions,[46] large lipids core and inflammation activity.[47] Nevertheless, the current study failed to prove the independent prognostic role of PR, though the incidence of MACE among group C was associated with a 2.4-fold increase among patients with plaque rupture. The discrepancy might be caused by insufficient follow-up time or small sample size. In addition, a small-size study of acute coronary syndrome cohort from Hu et al was in line with our results.[48] Due to the inconsistency on cardiovascular effect of plaque rupture, it

is warranted to conduct larger cohort studies to confirm the results.

Due to the lack of clinical and basic evidence, further studies are needed to confirm that PCSK9 may reflect thrombus type such as red, white or mixed thrombus or thrombus volume such as large or small number of thrombus. The possible mechanism can be explained as follows. The previous researches[29,49] have demonstrated that higher level of PCSK9 could lead to the inflammation of atherosclerosis by increasing infiltration of Ly6 monocytes in the plaque which supports the notion that PCSK9 inhibitors may improve cardiovascular outcomes through lipid independent and lipid-dependent pathways. The erosions of plaque trigger atherothrombosis by exposing thrombogenic material which inside the plaque, including matrix molecules, tissue factor, phospholipids and coagulation factors.[50] Atherothrombi can expand and fill the lumen rapidly which leading to infarction, ischemia and atherothrombosis.[42] The plaque with fibrous cap fracture more likely to have a larger lipid core and procoagulant tissue was localized among these cores.[43] Plaque erosion, another substrate for thrombus formation, shows less inflammatory cell accumulation which indicates exposed plaque constituents induce local hemorheology, activation systemic clotting activity, increased fibrinolytic function and sensitivity of the end organ to ischemia.[41] Therefore, pathogenetic mechanisms are different between these two types of plaque and should be considered separately. Disturbance of the balance between fibrinolysis activity and prothrombotic plays a significant role for precipitating the thrombotic event.[51] However, the precise sequence of events has not been known. Previous studies[52] have recognized thrombi involved on damaged vascular surfaces. Davies et al observed that ruptured plaques display large lipid core and thin fibrous caps regions. Furthermore, more studies[53,54] have revealed that culprit lesions of fatal thrombi in coronary arteries contain reduced amounts of mature and increased levels of collagen-degrading enzymes. Tissue factor which expressed by vascular smooth muscle cells in the atherosclerotic plaque could initiate the blood coagulation cascade that leads to fibrin formation.[55]

Mechanism

By motivating the adhesion of white blood cells and platelets to the vascular wall and stimulating plaque growth, elevated plasma levels of fibrinogen could accelerate the progression of atherosclerosis and raise the mortality.[51] It is worth noting that the expression of PCSK9 was increased in vascular smooth muscle cells at the sites of inflammation with low-shear stress.[38,56] From the mechanistic view, NADPH oxidase dependent reactive oxygen species, generated as by-products of the metabolism of molecular oxygen, mediated the circulating PCSK9 expression.[57] PCSK9 monoclonal antibodies (mAbs), including evolocumab and alirocumab which used to decrease the level of circulating PCSK9, are proven to provide substantial contributions for patients at very high risk of cardiovascular events.[58] The team of Kastelein et al[59] argued that ezetimibe might not share the lipid-independent effects of statins on anti-inflammatory properties and endothelial function. Previous study has demonstrated that PTX3 is strongly associated the incidence of cardiovascular and mortality among large Chinese cohort.[60] PTX3/P-selectin pathway has been identified to induce the vascular changes and they are implicated in the pathogenesis of vascular diseases such as plaque rupture, atherosclerosis, aortic aneurysms and neointimal hyperplasia.[61] Furthermore, previous studies has revealed that PTX3 induced an impairment in NO signaling that enhanced smooth muscle vasoconstriction and evoked endothelial dysfunction increasing vascular resistance.[62,63]

Our previous study[64] has found that patients with PR/high-PTX3 and PE/high-PTX3 presented a poorer prognosis than those with PE/low-PTX3. Combining the culprit-plaque morphology with PTX3 enhanced the predictive ability for MACE and contributed to better identification of high-risk patients. Furthermore, this research was conducted to verify the combination of PTX3 levels with plaque morphology to identify STEMI patients and revealed that plasma PTX3 and plaque rupture added important prognostic information. The team of Koga et al[15] has demonstrated that the frequency of TCFA significantly increased according to elevations in systemic PTX3 levels indicating that PTX3 is a useful biomarker to reflect coronary plaque vulnerability. What is more, higher levels of PTX3 were the most powerful predictor of TCFA in patients with stable angina pectoris and the entire study population. The typical morphology of TCFA is definite by a large necrotic core, large plaque burden, combining with thin-fibrous cap with infiltrating macrophages, and positive remodeling.[65] Nebuloni et al.[66] found that PTX3 localized in the interstitium of heart tissues of patients with AMI at autopsy is produced by endothelium, macrophages, to a lesser extent, myocardiocytes. Previous studies[67] have reported that PTX3 plays

a crucial part in the progression of atherosclerotic lesions by the soluble pattern recognition in innate immunity. Increasing levels of PTX3 has been confirmed that it could reflect a compensatory cardioprotective response to an activated inflammatory response.[68] The present result is in line with previous researches that elevated PTX3 is correlated with increased risk of MACE. The current findings may suggest higher prognostic value of PTX3 compared with PCSK9 in STEMI lesions with plaque erosion. In large cohort healthy adults from the Cardiovascular Health Study,[60] the results showed a strong positive association between level of PTX3 and incident all-cause death and cardiovascular disease.

Study Limitations

The present study has some limitations which must be given consideration. First, the use of a single baseline PCSK9 and PTX3 measurement which absence of evaluating effects of longitudinal changes during the follow-up period to predict outcomes did not allow us to assess the causal risk for incident cardiovascular endpoints. Therefore, further studies are warranted to clarify the mechanisms underlying the association between PCSK9 levels and PTX3. Thirdly, it is unclear whether our findings in STEMI individuals in China can be generalized to other diseases or other ethnicities and further prospective investigations among diverse populations, larger sample sizes, and studies with long-term follow-up should be undertaken.

Conclusion

Present study indicated that the combined measurement of PCSK9/PTX3 combined with morphology characteristics might add prognostic information and contribute to improve risk stratification among patients with STEMI. Patients with elevations of both PCSK9 and PTX3 have at least a 2.9-fold increased risk of MACE among all enrolled cohort and 9.04-fold increased risk of MACE among patients with plaque erosion. Further studies with a larger number of patients are needed to confirm these results.

Sponsor Role

Data Sharing Statement

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

It is from the ethics committee of the department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, China.

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Disclosure

No conflicts of interest, financial or otherwise, are declared by the authors.

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