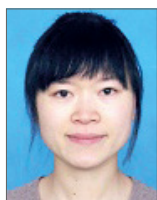# CORONARY INTERVENTIONS
## CLINICAL RESEARCH

# Pre-infarction angina and culprit lesion morphologies in patients with a first ST-segment elevation acute myocardial infarction: insights from in vivo optical coherence tomography

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## Abstract

**Aims:** This study aimed to evaluate the relationship between pre-infarction angina (PIA) and *in vivo* culprit lesion characteristics as assessed by intravascular optical coherence tomography (OCT) in patients with a first ST-segment elevation myocardial infarction (STEMI).

**Methods and results:** A total of 305 consecutive patients with a first STEMI who underwent OCT imaging of culprit lesions during primary percutaneous coronary intervention (PCI) were prospectively enrolled. OCT findings of the culprit plaque were compared between patients with (n=206) and without PIA (n=99). Patients with PIA showed lower rates of thin-cap fibroatheroma (TCFA) (62.6% vs. 80.8%, p=0.001) and plaque rupture (56.8% vs. 72.7%, p=0.007), smaller maximum ruptured cavity areas (1.10±1.04 mm² vs. 1.53±1.20 mm², p=0.002), and more severe residual luminal narrowing (p=0.015) with a higher incidence of white residual thrombus (68.4% vs. 50.0%, p=0.003) at the culprit lesions than patients without PIA. No significant differences in clinical outcomes were observed at the one-year follow-up.

**Conclusions:** In patients with a first STEMI, PIA was significantly associated with a lower incidence of TCFA and plaque rupture, a smaller ruptured cavity area, more white residual thrombi, and more severe lumen stenosis at the culprit lesions. Clinical Trials Identifier: NCT03107624

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## Abbreviations

**AMI**    acute myocardial infarction
**IFC**    intact fibrous cap
**IRA**    infarct-related artery
**OCT**    optical coherence tomography
**PCI**    percutaneous coronary intervention
**QCA**    quantitative coronary angiography
**STEMI**    ST-segment elevation myocardial infarction
**TCFA**    thin-cap fibroatheroma
**TIMI**    Thrombolysis In Myocardial Infarction

## Introduction

Pre-infarction angina (PIA) occurs frequently in patients with ST-segment elevation myocardial infarction (STEMI)[1]. Previous studies have shown that PIA is associated with smaller infarct sizes, preserved left ventricular function, reduced microvascular and myocardial damage and improved clinical prognoses[2-5]. Multiple mechanisms have been suggested to account for the myocardial protection of PIA in the setting of STEMI, including opening of pre-existing collateral vessels, an ischaemic myocardial conditioning effect, and different plaque morphologies at the culprit site limiting the thrombus burden[6-8]. Post-mortem and *in vivo* studies using intravascular ultrasound (IVUS) suggest that the composition of the culprit plaque may be different in patients presenting with PIA with less potent thrombogenicity from that in patients without PIA[9,10]. These studies were limited by case selection biases, small sample sizes and the inability of IVUS to assess intact fibrous cap (IFC) plaque and thrombus constituents. To date, significant uncertainty remains regarding the role of culprit plaque composition in the occurrence of PIA. Intracoronary optical coherence tomography (OCT) is a catheter-based imaging modality with a unique axial resolution (10 to 20 μm) that enables accurate *in vivo* detection and measurement of morphometric characteristics of the culprit lesion[11], including ruptured versus IFC plaques, the cap thickness of fibroatheroma, and thrombus constituents.

Based on these premises, we prospectively investigated the relationship between PIA and the *in vivo* characteristics of culprit lesions in a large cohort of consecutive patients with a first STEMI using OCT at the time of primary percutaneous coronary intervention (PCI).

## Methods

### STUDY DESIGN AND POPULATION

This study was a prospective observational study (NCT03107624) conducted in 305 consecutive patients presenting with a first STEMI at The Second Affiliated Hospital of Harbin Medical University between June 2016 and January 2017.

All patients underwent primary PCI within 12 hours of symptom onset. Pre-intervention OCT evaluation of the culprit lesion in the infarct-related artery (IRA) was performed in all patients immediately after restoring an effective antegrade coronary flow. Inclusion/exclusion criteria are listed in **Supplementary Appendix 1**. The study flow chart is shown in **Figure 1**.

The study was approved by the Ethics Review Committee of The Second Affiliated Hospital of Harbin Medical University, China, and all patients provided written informed consent before any procedure.

### SYMPTOM DATA COLLECTION

Detailed information regarding patients' clinical histories and symptoms, especially occurring in the month before the infarction, was collected in all cases before primary PCI. The information was assessed again within 48 hours after primary PCI and reported in a standardised questionnaire administered by researchers. Briefly, information regarding the presence or absence of angina, the patterns of angina and the time intervals between the last episode of chest pain and the onset of symptoms of acute myocardial infarction (AMI) was recorded.

### DEFINITION OF PIA

PIA was defined as at least one episode of angina (typical chest pain, chest discomfort or radiating pain), either at rest or during exercise, lasting less than 30 minutes, and occurring prior to the onset of infarction-related pain. Conversely, no PIA was defined as a sudden-onset STEMI without angina before infarction. Following the classification of previous studies[9,12], the type of PIA was further categorised as one of the following: 1) unstable PIA, defined as either new-onset (new development of angina during the month preceding infarction) or accelerated (angina that had been present for >1 month and had increased in severity during the month before infarction) angina; and 2) stable PIA, defined as angina that had been present for >1 month with no change in the angina pattern during the month before infarction. The timing of the closest episode of angina prior to myocardial infarction was divided into the following four categories: within 24 hours, between one and seven days, between seven days and one month, and more than one month before infarction.

### ANGIOGRAPHIC ANALYSIS

The details of the angiographic analysis are reported in **Supplementary Appendix 1**.

### OCT IMAGE ACQUISITION AND ANALYSIS

All OCT images were analysed using previously validated criteria[11]. Briefly, plaque rupture was identified by the presence of cavity formation in the culprit plaque with discontinuity of the fibrous cap[13]. An IFC culprit lesion was defined as the presence of a luminal thrombus overlying an intact cap fibroatheroma (definite erosion), or luminal surface irregularity at the culprit lesion in the absence of clear thrombus (possible erosion), or attenuation of an underlying plaque without superficial lipids or calcification immediately proximal or distal to the thrombus site[13]. Representative OCT images of culprit lesion features in patients with STEMI are presented in **Figure 2**.

The outlines of the lumen and flow areas were drawn for measurements on a cross-sectional image using the multiple-point trace
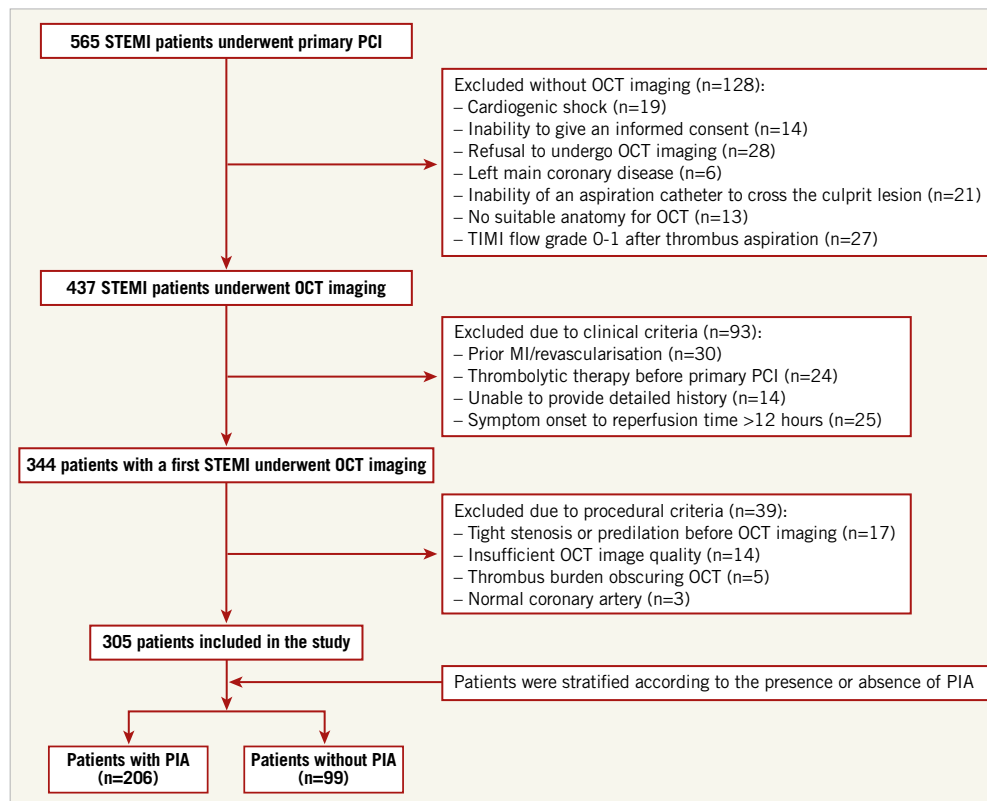
**Figure 1.** *Study flow chart. Out of 344 patients who presented with a first STEMI, 305 patients were identified as eligible for the study and were enrolled based on the inclusion/exclusion criteria. MI: myocardial infarction; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; PIA: pre-infarction angina; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction*

function. The lumen area and flow area were measured for each interval within the culprit lesion, and the thrombus area (TA) was defined as the lumen area minus the flow area for the entire measurable segment[14] **(Supplementary Figure 1A, Supplementary Figure 1B)**. The minimum lumen area (MLA) was defined as the smallest lumen area measured along the length of the culprit lesion. In ruptured plaques, quantitative measurements, including lumen area and ruptured cavity area, were performed using manual tracing at each frame interval (0.2 mm) throughout the ruptured plaque. The maximal ruptured cavity site was identified based on these tracings, and the ruptured cavity area at the site of the largest intra-plaque cavity was reported[15] **(Supplementary Figure 1C, Supplementary Figure 1D)**. The details of OCT imaging acquisition and analysis methods are reported in **Supplementary Appendix 1**.

#### CLINICAL OUTCOMES
Major adverse cardiovascular events (MACE) (i.e., the composite of cardiac death or recurrent myocardial infarction related to the target vessel, clinically driven target lesion revascularisation, and unstable angina requiring hospitalisation), and individual components of MACE were assessed at one year. The definitions of the individual components of MACE are summarised in **Supplementary Appendix 1**.

#### STATISTICAL ANALYSIS
Categorical data are expressed as counts and percentages and were compared using $\chi^2$ tests or Fisher's exact test. Continuous variables are presented as the mean±standard deviation and were compared using unpaired Student's t-tests. A p-value <0.05 was considered statistically significant. Interobserver and intra-observer variability was assessed using kappa statistics for the major morphometric OCT variables and intraclass correlation coefficients for continuous measurements. All statistical analyses were performed using SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

### Results
#### CLINICAL CHARACTERISTICS
STEMI onset with exertion was significantly less common in patients with PIA than in those without PIA **(Table 1)**. Infarct size, as determined by the peak creatine kinase-myocardial band (CK-MB) levels and peak troponin I levels, was smaller in patients with PIA than in those without PIA **(Table 1)**.

#### PIA CHARACTERISTICS
The PIA and clinical characteristics, and the angiographic and OCT findings according to the status of PIA are reported in
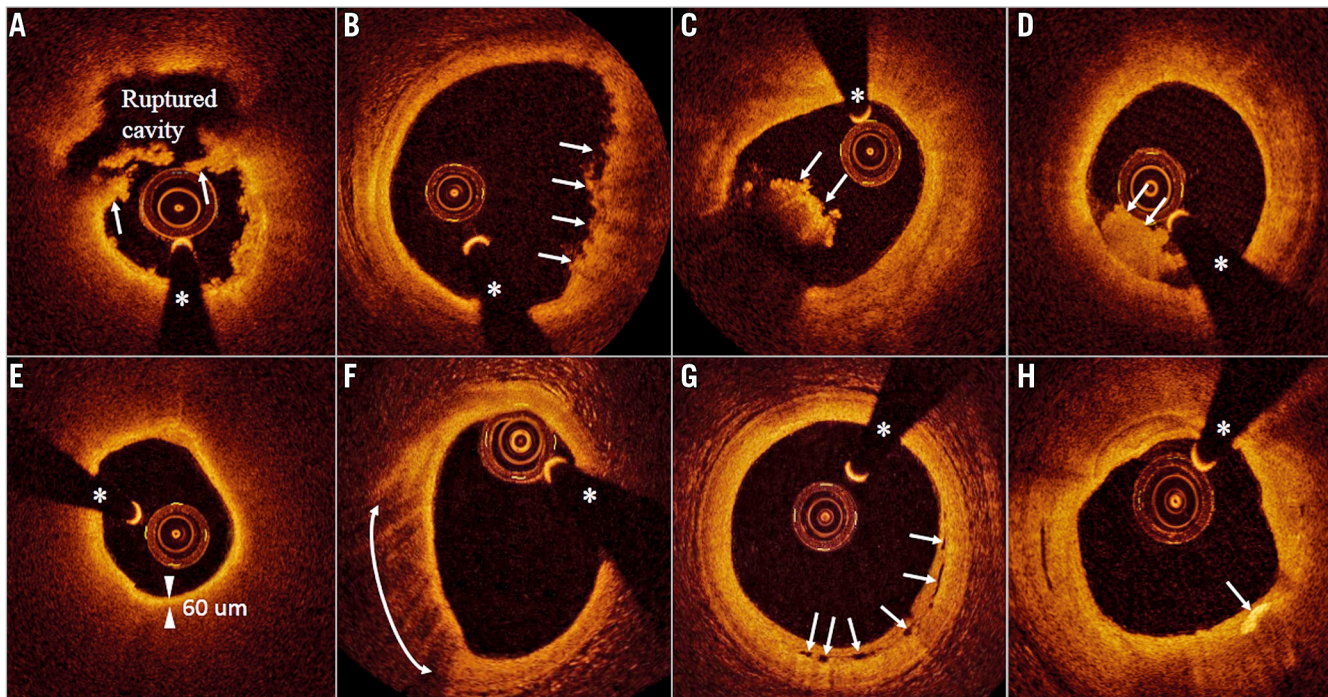
**Figure 2.** *Representative OCT images of culprit lesion features in patients with STEMI. A) Ruptured plaque with remnants of the fibrous cap (arrows), a ruptured cavity and small residual white thrombus masses. B) Intact fibrous cap (IFC) fibrous-lipidic plaque with small protruding thrombi (arrows). C) Red thrombus (arrows) protruding into the lumen with high signal backscattering and attenuation. D) White thrombus (arrows) protruding into the lumen with homogeneous signal backscattering and low attenuation. E) Thin-cap fibroatheroma (TCFA) with circumferential lipid constituents and low signal backscattering. A minimum cap thickness of 60 μm (two arrowheads) was measured. F) A lipid-rich plaque with a superficial signal-rich band and high signal attenuation identifying macrophages (arrows from six to nine o'clock). G) Microchannels (arrows) appear as multiple voids with low signal backscattering. H) A cholesterol crystal (arrow) appears as a linear, high-intensity signal within the plaque. The asterisk indicates the guidewire shadow. OCT: optical coherence tomography; STEMI: ST-segment elevation myocardial infarction*

**Supplementary Appendix 2**. The incidence and type of PIA are reported in **Supplementary Figure 2**. The time intervals between the last episode of angina and the STEMI onset in patients with PIA are shown in **Supplementary Figure 3**. Clinical characteristics, angiography, and OCT findings in patients without PIA and with unstable or stable PIA are provided in **Supplementary Table 1-Supplementary Table 3**.

### ANGIOGRAPHIC FINDINGS

Collateral vessels were more frequently observed in patients with PIA than in those without PIA, although the presence of good collaterals was not significantly different between the two groups **(Table 2)**.

### OCT FINDINGS

Patients with PIA exhibited a significantly lower incidence of thin-cap fibroatheroma (TCFA) and plaque rupture, a thicker minimal fibrous cap, a smaller lipid core, more white residual thrombi and more severe luminal narrowing at the culprit lesions than patients without PIA **(Table 3)**. The maximum ruptured cavity area and the MLA were significantly smaller in patients with PIA than

in patients without PIA **(Table 4)**. The interobserver and intraobserver kappa statistics for the qualitative assessment of plaque rupture/IFC were 0.917 and 0.922, respectively. The intraclass correlations for the maximum ruptured cavity area were 0.988 and 0.990, respectively.

### CLINICAL OUTCOMES

Clinical follow-up data were available for 301 of the 305 patients (98.7%). The median follow-up time was 13.8±3.8 months. No significant differences in clinical outcomes were observed at the one-year follow-up **(Supplementary Table 4)**.

## Discussion

This is the first *in vivo* study to compare prospectively the culprit lesion phenotypes observed by OCT in patients with a first STEMI with or without PIA. The main findings are as follows: PIA occurred frequently in patients with a first STEMI and was significantly associated with a thicker fibrous cap, smaller lipid arc, fewer TCFAs, lower incidences of plaque rupture and red residual thrombi, smaller rupture cavities, and more severe luminal narrowing at the sites of culprit lesions.

**Table 1. Clinical characteristics.**

| Variable | Patients with PIA (n=206) | Patients without PIA (n=99) | p-value |
|---|---|---|---|
| Age, years | 57±10 | 58±11 | 0.589 |
| Men, n (%) | 145 (70.4) | 78 (78.8) | 0.121 |
| BMI, kg/m² | 25.17±3.59 | 24.69±3.63 | 0.289 |
| Time from symptom onset to reperfusion, min | 288±179 | 296±156 | 0.698 |
| STEMI onset upon exertion, n (%) | 122 (59.2) | 80 (80.8) | <0.001 |
| Risk factors, n (%) | | | |
|   Hypertension | 110 (53.4) | 40 (40.4) | 0.034 |
|   Dyslipidaemia | 129 (62.6) | 66 (66.7) | 0.491 |
|   Diabetes mellitus | 60 (29.1) | 26 (26.3) | 0.603 |
|   Current smoking | 127 (61.7) | 71 (71.7) | 0.085 |
|   Family history of CAD | 73 (35.4) | 32 (32.3) | 0.592 |
| Prior medications, n (%) | | | |
|   Aspirin | 20 (9.7) | 4 (4.0) | 0.085 |
|   Clopidogrel | 2 (1.0) | 0 (0) | 1.000 |
|   Statins | 4 (1.9) | 3 (3.0) | 0.552 |
|   Insulin | 21 (10.2) | 8 (8.1) | 0.556 |
| LVEDD, mm | 45.94±4.63 | 45.74±4.57 | 0.723 |
| LVEF, % | 58.76±5.61 | 58.36±6.11 | 0.582 |
| Laboratory results | | | |
|   Total cholesterol, mg/dL | 191.29±38.85 | 187.84±37.65 | 0.471 |
|   LDL-C, mg/dL | 123.34±34.53 | 120.08±35.87 | 0.455 |
|   HDL-C, mg/dL | 49.94±10.78 | 47.96±12.36 | 0.161 |
|   Triglyceride, mg/dL | 151.44±115.47 | 167.73±137.00 | 0.315 |
|   HbA1c, % | 6.30±1.30 | 6.28±1.54 | 0.927 |
|   eGFR, ml/min/1.73 m² | 92.03±22.20 | 92.72±21.62 | 0.798 |
|   Peak CK-MB, µg/L | 203.73±196.77 | 255.47±223.89 | 0.033 |
|   Peak troponin I, µg/L | 91.95±102.77 | 120.90±120.04 | 0.025 |

Values are presented as mean±SD or n (%). BMI: body mass index; CAD: coronary artery disease; CK-MB: creatinine kinase-myocardial band; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; PIA: pre-infarction angina; STEMI: ST-segment elevation myocardial infarction

**Table 2. Angiographic findings.**

| Variable | | Patients with PIA (n=206) | Patients without PIA (n=99) | p-value |
|---|---|---|---|---|
| Infarct-related artery, n (%) | LAD | 108 (52.4) | 44 (44.4) | 0.399 |
| | LCX | 19 (9.2) | 12 (12.1) | |
| | RCA | 79 (38.4) | 43 (43.4) | |
| Multivessel disease, n (%) | | 113 (54.9) | 49 (49.5) | 0.380 |
| TIMI flow grade at presentation, n (%) | 0 | 149 (72.3) | 72 (72.7) | 0.655 |
| | 1 | 5 (2.4) | 4 (4.0) | |
| | 2 | 30 (14.6) | 16 (16.2) | |
| | 3 | 22 (10.7) | 7 (7.1) | |
| Thrombus aspiration, n (%) | | 181 (87.9) | 93 (93.9) | 0.100 |
| TIMI flow grade after thrombus aspiration, n (%) | 2 | 65 (31.6) | 27 (27.3) | 0.446 |
| | 3 | 141 (68.4) | 72 (72.7) | |
| TIMI flow grade end procedure, n (%) | 0/1 | 0 (0.0) | 1 (1.0) | 0.347 |
| | 2 | 18 (8.7) | 8 (8.1) | |
| | 3 | 188 (91.3) | 90 (90.9) | |
| QCA analysis at baseline | MLD, mm | 0.17±0.35 | 0.18±0.39 | 0.885 |
| | Diameter stenosis, % | 93.49±12.66 | 93.51±13.39 | 0.993 |
| QCA analysis after thrombus aspiration | RVD, mm | 2.82±0.51 | 2.91±0.82 | 0.267 |
| | MLD, mm | 1.07±0.44 | 1.15±0.43 | 0.150 |
| | Lesion length, mm | 14.16±7.13 | 12.68±4.56 | 0.074 |
| | Diameter stenosis, % | 62.02±14.45 | 57.78±16.74 | 0.033 |
| | MLD end procedure, mm | 1.97±0.91 | 1.99±0.82 | 0.888 |
| Rentrop grade for collaterals, n (%) | 0 | 105 (51.0) | 65 (65.7) | 0.101 |
| | 1 | 60 (29.1) | 18 (18.2) | |
| | 2 | 29 (14.1) | 11 (11.1) | |
| | 3 | 12 (5.8) | 5 (5.1) | |
| Presence of collaterals, n (%) | | 101 (49.0) | 34 (34.3) | 0.016 |
| Presence of good collaterals, n (%) | | 41 (19.9) | 16 (16.2) | 0.433 |

Values are presented as mean±SD or n (%). LAD: left anterior descending; LCX: left circumflex artery; MLD: minimum lumen diameter; PIA: pre-infarction angina; QCA: quantitative coronary angiography; RCA: right coronary artery; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

## PIA: INCIDENCE AND IMPACT ON INFARCT SIZE

In this study, the incidence of PIA in patients with a first STEMI was 68%. It has been demonstrated that many patients suffering from AMI may experience PIA in the hours, days, or weeks preceding the acute coronary event[12]. The reported incidence of PIA in the literature varies from 10% to 69%, reflecting an extremely broad span that may be related to differences in the definitions of PIA, the study populations recruited, or the methods used to collect patient information[12,16]. In our prospective study, we confirmed that unstable patterns of PIA are very common in patients presenting with a first STEMI, with 80% of cases of instability occurring within one week of myocardial infarction.

Numerous studies conducted in STEMI patients have shown associations of PIA with smaller infarct size, preserved left ventricular function, less microvascular damage and better clinical outcomes[2-5]. The beneficial effects of PIA have been proposed to be related to ischaemic preconditioning, the development of collateral vessels, improved reperfusion and preserved microvascular circulation[4,6-8]. The results of the present study support existing data indicating that PIA is associated with smaller infarct sizes and a higher incidence of collaterals in patients with a first STEMI. The lack of significant differences in the degree of collaterals and the presence of good collaterals between patients with and without PIA could be explained by the exclusion of patients with prior myocardial infarction or prior coronary interventions. In our study, a low rate of target vessel-related events with no difference in outcome was observed at the one-year follow-up. The high success rate of reperfusion achieved with primary PCI in both groups with normal ejection fraction and preserved left ventricular diameters may have concealed further differences in outcome.

**Table 3. OCT findings at the culprit lesion site.**

| Variable | | Patients with PIA (n=206) | Patients without PIA (n=99) | p-value |
|---|---|---|---|---|
| **Qualitative analysis** | | | | |
| Plaque composition, n (%) | Fibrous plaque | 28 (13.6) | 9 (9.1) | 0.260 |
| | Lipid-rich plaque | 178 (86.4) | 90 (90.9) | |
| TCFA, n (%) | | 129 (62.6) | 80 (80.8) | 0.001 |
| Plaque morphology, n (%) | Rupture | 117 (56.8) | 72 (72.7) | 0.007 |
| | IFC | 89 (43.2) | 27 (27.3) | |
| Residual thrombus, n (%) | | 190 (92.2) | 92 (92.9) | 0.829 |
| Thrombus type, n (%) | White thrombus | 130 (68.4) | 46 (50.0) | 0.003 |
| | Red thrombus | 60 (31.6) | 46 (50.0) | |
| Macrophages, n (%) | | 180 (87.4) | 89 (89.9) | 0.523 |
| Cholesterol crystals, n (%) | | 90 (43.7) | 41 (41.4) | 0.707 |
| Microchannels, n (%) | | 73 (35.4) | 38 (38.4) | 0.617 |
| Calcification, n (%) | | 62 (30.1) | 23 (23.2) | 0.211 |
| **Quantitative analysis** | | | | |
| Minimal FCT, μm | | 69.42±28.21 | 58.00±17.40 | 0.001 |
| Maximal lipid arc, ° | | 274.56±65.58 | 294.07±67.58 | 0.024 |
| Thrombus length, mm | | 4.95±3.40 | 5.20±3.26 | 0.559 |
| Average thrombus area, mm² | | 0.51±0.41 | 0.61±0.54 | 0.111 |
| Maximal thrombus area, mm² | | 0.96±0.86 | 1.19±1.02 | 0.050 |
| Thrombus volume, mm³ | | 3.11±4.16 | 3.79±5.28 | 0.277 |
| Mean reference vessel area, mm² | | 7.10±2.90 | 6.97±2.43 | 0.686 |
| MLA, mm² | | 1.80±1.03 | 2.13±1.29 | 0.029 |
| Lumen area stenosis, % | | 72.88±12.50 | 68.34±16.22 | 0.015 |

Values are presented as mean±SD or n (%). FCT: fibrous cap thickness; IFC: intact fibrous cap; MLA: minimum lumen area; OCT: optical coherence tomography; PIA: pre-infarction angina; TCFA: thin-cap fibroatheroma

**Table 4. OCT findings of plaque rupture in 189 patients.**

| Variable | | Patients with PIA (n=117) | Patients without PIA (n=72) | p-value |
|---|---|---|---|---|
| Maximum ruptured cavity area, mm² | | 1.10±1.04 | 1.53±1.20 | 0.002 |
| Lumen area at maximum ruptured cavity site, mm² | | 3.48±2.43 | 3.59±2.15 | 0.773 |
| MLA, mm² | | 1.83±0.96 | 2.26±1.21 | 0.007 |
| Lumen area stenosis, % | | 72.92±12.62 | 67.08±16.24 | 0.006 |
| Location of the maximum ruptured cavity, n (%) | Proximal to the MLA site | 76 (65.0) | 56 (77.8) | 0.172 |
| | At the MLA site | 27 (23.1) | 11 (15.3) | |
| | Distal to the MLA site | 14 (12.0) | 5 (6.9) | |

Values are presented as mean±SD or n (%). MLA: minimum lumen area; OCT: optical coherence tomography; PIA: pre-infarction angina

and the more frequent myocardial infarction induced by exertion observed in patients without PIA could explain the higher rate of plaque rupture and the larger ruptured cavity area in these patients.

## PIA AND THROMBUS COMPONENTS

In the current study, we did not observe any difference in thrombus volume between patients with and without PIA after manual thrombectomy. However, we found differences in thrombus composition. Patients with PIA had significantly more white (platelet-rich) thrombi, while those without PIA had more red (erythrocyte-rich) residual thrombi. Differences in culprit plaque characteristics might have contributed considerably to the difference in thrombus composition observed in patients with/without PIA. We noticed a greater intrinsic plaque vulnerability (thinner cap with larger lipid core) and increased incidence of plaque rupture in patients without PIA and a higher rate of IFC atheroma in patients with PIA. We showed in prior studies that ruptured plaques are mostly associated with red thrombi while eroded plaques without rupture are preferentially accompanied by white thrombi[13,20]. The difference in thrombus components detected by OCT between patients with and without PIA is consistent with these pathophysiological principles.

## PIA AND LESION SEVERITY

The current OCT study demonstrated that PIA is associated with more severe lumen narrowing than that observed in patients without PIA, which agrees with the results of a prior study[21]. Although the difference in lesion severity between the two groups was statistically significant, the difference was marginal from a clinical standpoint. In this study, patients without PIA showed less severe luminal narrowing but a larger lipid arc with a higher incidence of TCFA at the culprit site. This result suggests that attained compensatory enlargement could be responsible for preventing significant stenosis; however, lesions with a large plaque burden and positive remodelling may be more vulnerable to rupture leading to sudden thrombotic occlusion. Consistent with the results of a previous study[22], we found that most STEMI events occur in the presence of significant lumen stenosis regardless of the presence

## PIA AND PLAQUE MORPHOLOGIES

Consistent with all previous investigations, we found that plaque rupture was the most common cause of coronary thrombosis in STEMI, regardless of the presence or absence of PIA[17]. However, in patients with PIA, we observed a lower incidence of TCFA and plaque rupture, a smaller lipid core with a smaller rupture cavity area and a significantly thicker fibrous cap than in patients without PIA, despite similar lipid-rich culprit plaque constituents. Further, patients with PIA less frequently experienced the symptom onset upon exertion compared with those without PIA, in line with the results of a prior study[18]. This observation may simply reflect a reduced daily physical activity in patients with PIA, especially those with rest angina. Rupture of a TCFA and subsequent thrombosis may occur spontaneously but, in some cases, a temporary increase in emotional or physical stress may act as a final trigger for the clinical event[19]. In our study, patients with sudden onset of STEMI without anticipating angina had a significantly thinner fibrous cap and larger lipid core with a higher incidence of TCFA than patients with PIA, suggesting that patients without PIA may have a lower threshold for abrupt coronary occlusion due to greater vulnerability of the underlying plaque than patients with anticipatory symptoms. The greater intrinsic plaque vulnerability (thinner cap with larger lipid core)

or absence of PIA. Histopathological findings reported in some cases of AMI with PIA showed that the arterial lumen was partially narrowed by an old healed atheroma with organised thrombus[23]. Such a pathological process might be a possible explanation for the more severe luminal narrowing observed in patients with PIA compared with patients without PIA.

## Limitations

This study has several limitations. First, this was an observational study conducted at a single centre. Although the data were prospectively collected and all patients were consecutively enrolled, several patients were excluded from the current analysis, possibly resulting in case selection bias. Therefore, this study cannot be generalised to all patients presenting with STEMI. Second, in patients with TIMI flow grade 0/1 or large angiographic filling defects, manual thrombectomy was performed to re-establish effective vessel patency, allowing safe and high-quality OCT imaging data collection at the culprit site. However, the potential effect of the thrombus aspiration catheter on superficial plaque integrity and atherothrombotic components assessed by OCT must be given serious consideration. Third, the clinical descriptions of the symptoms characterising PIA were subjective. Although the use of a standardised questionnaire administered by researchers at multiple time points near the acute event to confirm the data on PIA may have improved the reporting quality, uncertainties remain regarding the reliability of our group classifications. Fourth, histopathological examination of thrombus aspirates was not performed. Therefore, no conclusions can be drawn regarding the relationships of thrombus compositions to the presence and type of PIA. Fifth, because a large residual thrombus burden at the culprit site may obscure the underlying plaque morphology and impede accurate measurement of the lumen area, we excluded patients with massive residual thrombus precluding visualisation from the analysis.

## Conclusions

The present study demonstrates that patients with a first STEMI and PIA have a significantly lower incidence of TCFA and plaque rupture, a smaller ruptured cavity area, more white residual thrombi, and more severe lumen stenosis at the culprit lesion compared with patients without PIA.

### Impact on daily practice

Differences in the *in vivo* culprit lesion morphologies observed in STEMI patients with PIA may suggest different underlying pathophysiological mechanisms that may eventually enable tailored treatment strategies. Additional studies are warranted to elucidate better the impact of PIA on the development of STEMI. Increased public awareness of the clinical relevance of prodromal symptoms that precede STEMI is needed, especially in large countries where primary PCI systems are currently being developed.

## Conflict of interest statement

The authors have no conflicts of interest to declare.

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## Supplementary data

**Supplementary Appendix 1.** Methods.

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**Supplementary Figure 1.** Methods for the quantitative assessment of ruptured plaques and thrombi on OCT images.

**Supplementary Figure 2.** Incidence and type of PIA in patients with a first STEMI.

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**Supplementary Table 1.** Patient clinical characteristics according to the status of PIA.

**Supplementary Table 2.** Angiographic findings according to the status of PIA.

**Supplementary Table 3.** OCT findings according to the status of PIA.

**Supplementary Table 4.** Clinical outcomes at the 1-year follow-up.

*The supplementary data are published online at:*
*http://www.pcronline.com/*
*eurointervention/150th_issue/305*

**Supplementary data**

**Supplementary Appendix 1. Methods**

*Inclusion criteria*

Patients who participated in this study met all of the following clinical inclusion criteria:

1. Male or non-pregnant female patients aged >18 years with acute myocardial infarction (AMI), defined as prolonged chest pain for more than 30 minutes, unresponsive to nitroglycerine;

2. ECG evidence of ST-segment elevation myocardial infarction (STEMI), defined as ST-segment elevation of ≥1 mm in two or more contiguous leads or new left bundle branch block;

3. Eligible for primary percutaneous coronary intervention (PCI);

4. Able and willing to provide written informed consent;

5. De novo, acute infarct culprit lesion located in a native coronary artery, eligible for optical coherence tomography (OCT) imaging and PCI.

*Exclusion criteria*

Patients meeting any of the following criteria at screening or during the angiographic procedure were excluded from study participation.

Clinical exclusion criteria:

1. Time from symptom onset to reperfusion >12 hours;

2. Prior bypass graft in the target lesion-related artery;

3. Prior myocardial infarction;

4. Thrombolytic therapy before primary PCI;

5. Unable to provide a detailed clinical history;

6. Cardiogenic shock (BP <80 mmHg for >30 minutes) or uncontrollable heart failure on admission;

7. Severe hepatic or renal insufficiency;

8. Inability to provide informed consent or refusal to undergo OCT imaging;

9. Any significant medical condition that, in the investigator's opinion, may interfere with the patient's optimal participation in the study.

Angiographic and OCT exclusion criteria:

1. Unprotected left main coronary artery disease with ≥50% stenosis;
2. Angiographic evidence of spontaneous dissection of the culprit vessel;
3. No suitable anatomy for OCT (extreme tortuosity and very distal culprit lesion);
4. Thrombolysis In Myocardial Infarction (TIMI) flow grade 0-1 after thrombus aspiration;
5. Inability of a thrombus aspiration catheter (when required) to cross the culprit lesion;
6. Predilation with balloon angioplasty and stenting before OCT imaging;
7. Insufficient OCT image quality;
8. Residual thrombus burden obscuring OCT;
9. Normal coronary artery.

***Measurement of creatine kinase-myocardial band (CK-MB) and troponin I (TnI)***

Blood samples for measuring CK-MB and TnI plasma levels were collected on admission to the hospital and every 6 hours for the first 24 hours after primary PCI. Subsequently, these levels were determined every day for at least 3 days or until discharge, unless clinical events prompted repeat measurements. Peak levels of CK-MB and TnI were calculated as a measure of the infarct size in each patient.

***Angiographic analysis***

Coronary angiograms were analysed using a validated automated edge-detection algorithm (CAAS II; Pie Medical, Maastricht, the Netherlands) by two expert readers blinded to the patients' clinical presentations. The infarct-related artery (IRA) was identified by analysing patients' electrocardiographic findings, left ventricular wall motion abnormalities, and angiographic lesion morphologies. Quantitative coronary angiography (QCA) was performed in the IRA to measure the reference vessel diameter (proximal and distal), minimum lumen diameter, and percent diameter stenosis at the culprit site. The TIMI flow grade of the IRA was assessed before and after thrombectomy, and the collateral flow towards the IRA was assessed using the Rentrop scoring system. Grade 2 or 3 collateral flow was defined as good collateral flow.

***OCT image acquisition***

The OCT images were acquired in the culprit vessel with a frequency-domain OCT system (ILUMIEN™ Optis™ OCT Imaging System; St. Jude Medical, St. Paul, MN, USA) immediately after flow restoration with the OCT catheter (C7 Dragonfly™; LightLab Imaging Inc./St. Jude Medical, Westford, MA, USA), which was positioned in the infarct-related coronary artery distal to the culprit lesion. Briefly, in patients with TIMI flow grade 0/1 or a large filling defect at the culprit site, manual thrombus aspiration was performed to re-establish the effective vessel patency with TIMI flow grade 2-3 before the OCT pullback. Patients with TIMI flow grade 2-3 at presentation and no filling defect underwent direct OCT pullback. No balloon predilation was allowed before the OCT assessment. OCT pullback (single or multiple) was performed using automated pullback at 20 mm/s. During image acquisition, continuous flushing of the contrast media injected through the guiding catheter at a rate of 3-4 mL/s was performed to obtain clear images by creating a virtually blood-free environment.

All patients received standard antithrombotic (heparin 70 IU/kg iv bolus) and antiplatelet (aspirin 300 mg orally and ticagrelor 180 mg loading dose) therapy before undergoing primary PCI. Decisions regarding the use of glycoprotein IIb/IIIa inhibitors and the treatment of the culprit lesion were left to the discretion of the interventionalists.

### OCT image analysis

All OCT images were digitally recorded and stored before the offline analysis performed at the Imaging Core Laboratory (Cardiovascular Department of the 2nd Affiliated Hospital of Harbin Medical University). Two OCT expert readers (R.S. and S.Z.), unaware of the patients' clinical and angiographic characteristics, initially screened the images for quality and then performed qualitative and quantitative OCT analyses using proprietary software (OCT Offline Review Workstation; LightLab Imaging Inc.). Any disagreement was resolved by consensus. All adopted OCT parameters for plaque morphology and morphometric assessments were based on previously accepted and validated criteria [11].

Plaque rupture was defined by the presence of cavity formation in the culprit plaque with discontinuity of the fibrous cap [13] **(Figure 2A)**. An intact fibrous cap (IFC) culprit lesion was defined as the presence of a luminal thrombus overlying an intact cap fibroatheroma (definite erosion), a luminal surface irregularity at the culprit lesion in the absence of clear thrombus (possible erosion), or attenuation of an underlying plaque by a thrombus without

superficial lipids or calcification immediately proximal or distal to the thrombus site [13] **(Figure 2B)**. An intracoronary thrombus was identified as an intraluminal mass with an irregular contour protruding into the lumen that was >250 µm at the thickest point, connected or not connected to the intimal surface. Red thrombi appeared as masses with high backscattering and high attenuation **(Figure 2C)**, while white thrombi appeared as homogeneous masses with less backscattering and low attenuation **(Figure 2D)**. Plaques were classified as lipid plaques, fibrous plaques, or calcific plaques based on the predominant constituents. A lipid plaque was defined as a signal-rich fibrous cap with poorly delineated borders exhibiting attenuation. A lipid-rich plaque was defined as a plaque containing lipids visible in at least two adjacent quadrants of any image of the plaque. A thin-cap fibroatheroma (TCFA) was defined as a lipid-rich plaque with a fibrous cap thickness of <65 µm **(Figure 2E)**. Fibrous plaque was defined as a homogeneous plaque with high backscattering and low attenuation. Calcifications appeared as regions with low scattering and sharp borders. Areas of macrophage infiltration appeared as signal-rich, distinct or confluent punctuate regions with heterogeneous backward shadows **(Figure 2F)**. Microchannels appeared as tubular or vesicular structures with diameters of 50-300 µm that were present in at least three consecutive frames **(Figure 2G)**. Cholesterol crystals appeared as linear, signal-rich structures adjacent to plaques **(Figure 2H)**.

For each lipid plaque, lipid length, maximum lipid arc, and minimum fibrous cap thickness were measured. The lipid length was calculated from the number of consecutive frames with dominant lipid plaque constituents. The lipid arc was measured every 1 mm, and the maximum value was reported. The minimum fibrous cap thickness was measured at the thinnest part of the cap and was reassessed three times, and the average was then calculated. The outlines of the lumen and flow areas were drawn for measurements on a cross-sectional image using the multiple-points trace function. The lumen and flow areas were measured by manual trace for each interval within the culprit lesion, and the thrombus area (TA) was defined as the lumen area minus the flow area for the entire measurable segment [14] **(Supplementary Figure 1A, Supplementary Figure 1B)**. The minimum lumen area (MLA) was defined as the smallest lumen area measured along the length of the culprit lesion. In principle, the nearest frame with luminal border visibility was used to guide the tracing of the lumen area in those frame segments where the luminal border was not visible due to shadowing by a red thrombus [14]. The thrombus volume was calculated by multiplying the mean thrombus area by the thrombus length. Proximal and distal references were measured at

the site with the largest lumen within 5 mm proximal and distal to the culprit lesion. The adopted RLA was calculated as the average of the proximal and distal RLAs. The percent area of stenosis was calculated using the following equation: (RLA - MLA) / RLA × 100. In ruptured plaques, the minimum fibrous cap thickness was measured at the thinnest point of the remnant cap, whereas the mean cap thickness was computed as the mean of 3 evenly distributed measurements along the fibrous cap. The quantitative measurements, including lumen area and ruptured cavity area, were performed using manual tracing at each frame interval (0.2 mm) throughout the ruptured plaque. The maximal ruptured cavity site was decided based on these tracings and the ruptured cavity area at the site of the largest intraplaque cavity was reported [15] (**Supplementary Figure 1C, Supplementary Figure 1D**).

*Definitions of major adverse cardiovascular events*

A major adverse cardiovascular event (MACE) was defined as the composite of cardiac death related to the target vessel, recurrent myocardial infarction related to the target vessel, clinically driven target lesion revascularisation (TLR), and unstable angina requiring hospitalisation. Cardiac death was defined as death from myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormalities, procedural complications, or any death in which a cardiac cause could not be excluded. Recurrent myocardial infarction related to the target vessel was defined as newly occurring myocardial infarction confirmed by coronary angiography and revealing the target vessel as the culprit lesion, or by electrocardiogram indicating new abnormal ST-T changes and/or left bundle branch block related to the target vessel. Clinically driven TLR was defined as either repeat percutaneous or surgical revascularisation with symptoms of a lesion anywhere within the stent or the 5-mm borders proximal or distal to the stent. Unstable angina requiring hospitalisation was defined as (1) ischaemic discomfort (angina or symptoms thought to be equivalent to angina) ⩾10 minutes in duration occurring at rest or occurring in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity, (2) unscheduled hospitalisation within 24 hours of the most recent symptoms, (3) negative cardiac biomarkers and no evidence of acute MI, and (4) at least one of the following: a) new or worsening ST or T-wave changes on a resting ECG (in the absence of confounders, such as LBBB or LVH); b) definitive evidence of inducible myocardial ischaemia; c) angiographic evidence of a new or ⩾70% lesion (⩾50% for left main lesions)

and/or a thrombus in the epicardial coronary artery that was believed to be responsible for the myocardial ischaemic symptoms/signs; and d) the need for a coronary revascularisation procedure (PCI or CABG) for the presumed culprit lesion(s).

**Supplementary Appendix 2. Results**

*PIA characteristics*

The incidence and type of PIA in patients with a first STEMI are reported in **Supplementary Figure 2**. Among 305 patients with a first STEMI, 206 patients (68%) experienced PIA, including 175 patients (58%) who experienced unstable angina before STEMI onset and 31 patients (10%) who indicated only stable angina. The remaining 99 patients (32%) did not experience angina before the infarction. Among 175 patients with unstable angina, 130 (43%) experienced new-onset angina, and 45 (15%) experienced accelerated angina.

The time intervals between the last episode of angina and STEMI onset in patients with PIA are reported in **Supplementary Figure 3**. Among 206 patients with PIA, 113 patients (55%) experienced PIA within 24 hours, 51 patients (25%) between 1 and 7 days, 26 patients (12%) between 7 and 30 days, and 16 patients (8%) more than 1 month before infarction. In patients with PIA, instability occurred within 1 week of myocardial infarction in 80% of cases.

*Clinical characteristics, angiography and OCT findings in patients without PIA and with unstable or stable PIA*

No significant differences were observed in clinical and laboratory results among the three groups, except STEMI onset with exertion, which was significantly less common in patients with unstable or stable PIA than in those without PIA **(Supplementary Table 1)**.

Culprit lesion site, lesion length and severity, and TIMI flow grade at presentation did not differ among the 3 groups. Although collateral vessels were more frequently observed in STEMI patients with stable or unstable PIA before infarction than in STEMI patients without PIA, there was no significant difference **(Supplementary Table 2)**.

The qualitative and quantitative OCT findings observed at the culprit plaque site in the 3 groups are reported in **Supplementary Table 3**. Patients with PIA (either stable or unstable) exhibited a similarly high rate of lipid-rich plaques but a significantly thicker fibrous cap and a lower incidence of TCFA than patients without PIA. Patients with unstable PIA had a significantly lower incidence of plaque rupture, a smaller ruptured cavity area, more white residual thrombi and more severe lumen area stenosis than patients without PIA.
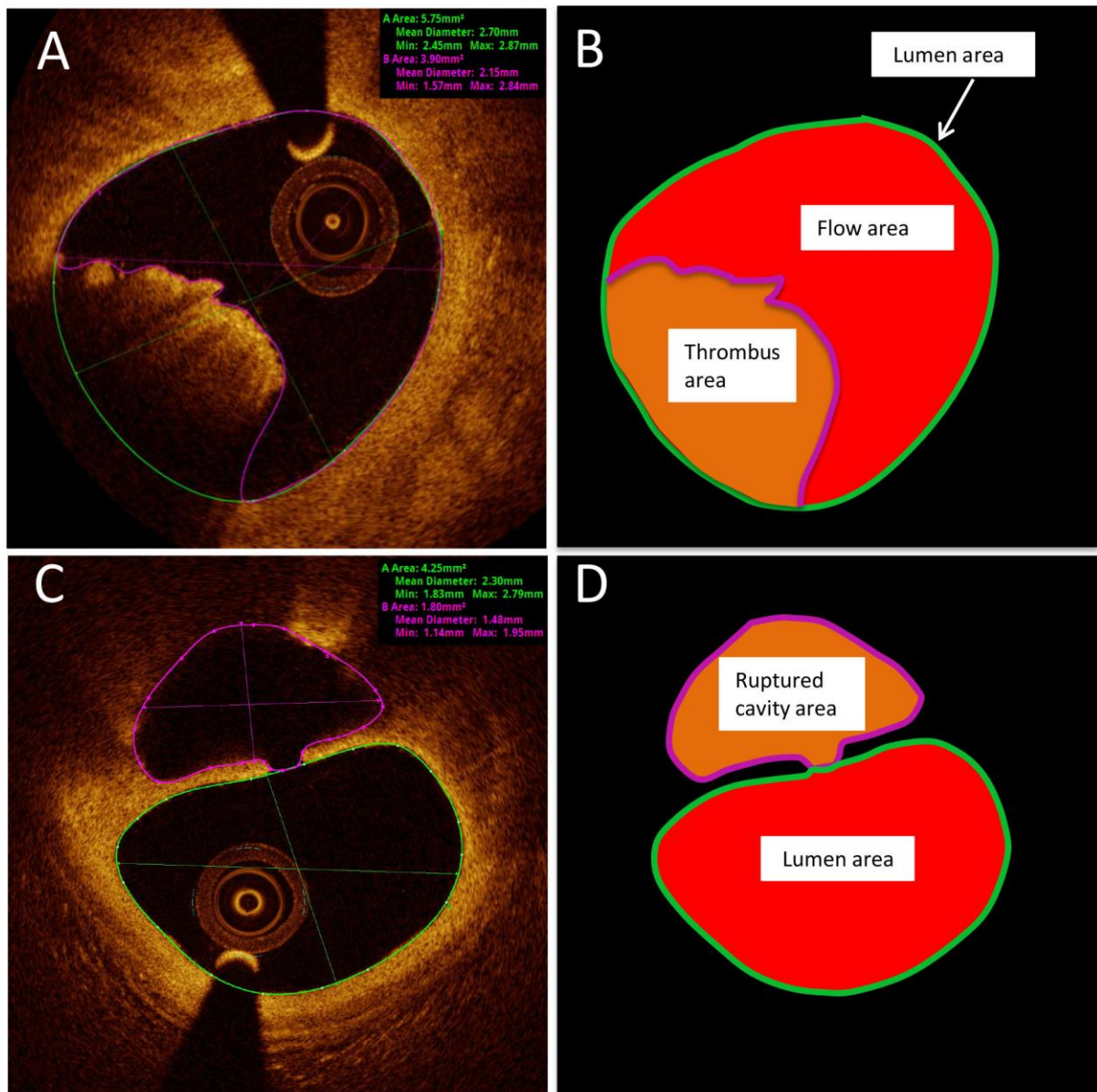
**Supplementary Figure 1.** Methods for the quantitative assessment of ruptured plaques and thrombi on OCT images.

A) Actual measurements of the lumen and flow areas at a thrombus site on a sample cross-section of the OCT pullback. B) A schematic representation of the flow and thrombus area is shown. On each cross-section, the thrombus area (mm$^2$) = lumen area (mm$^2$)–flow area (mm$^2$). C) Actual measurements of the lumen and ruptured cavity areas at the ruptured site using the proprietary offline review workstation software (LightLab Imaging Inc.) on a sample cross-section of the OCT pullback. D) Schematic representation of the lumen area and ruptured cavity area. OCT: optical coherence tomography
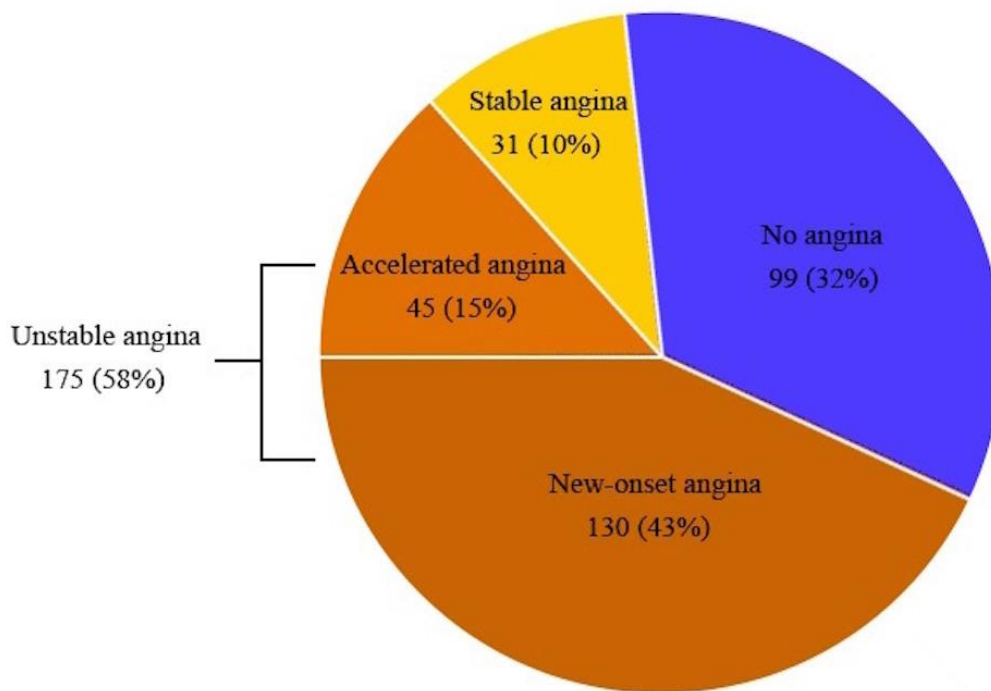
**Supplementary Figure 2.** Incidence and type of PIA in patients with a first STEMI.

PIA: pre-infarction angina; STEMI: ST-segment elevation myocardial infarction
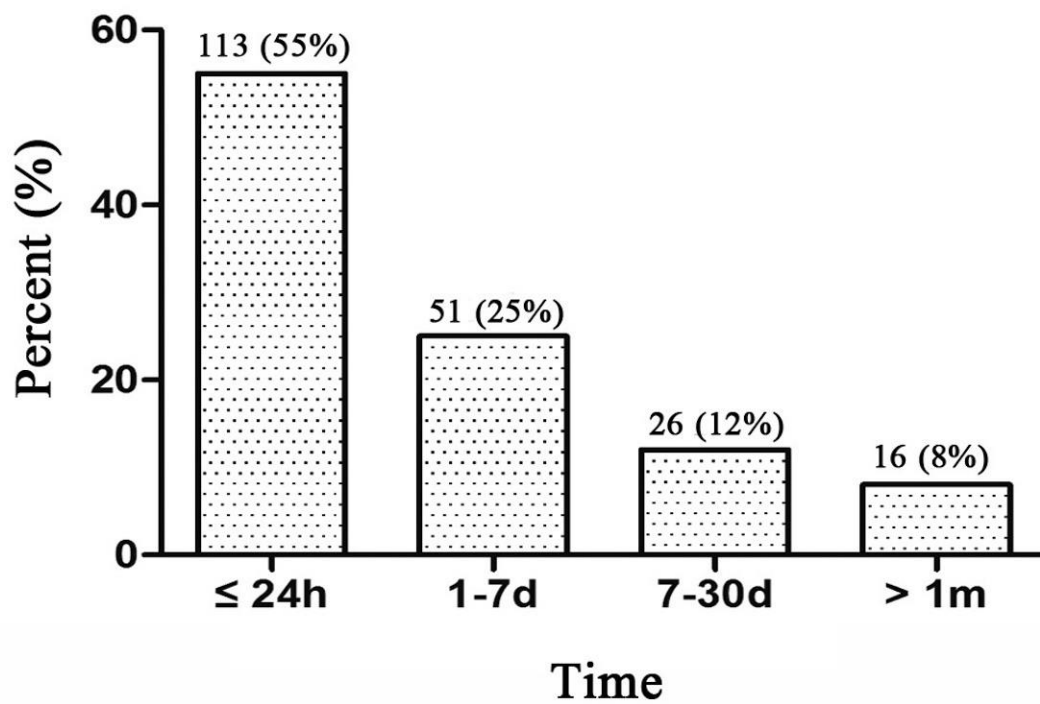
**Supplementary Figure 3.** Time interval between the last episode of angina and STEMI onset in patients with PIA.

PIA: pre-infarction angina; STEMI: ST-segment elevation myocardial infarction

**Supplementary Table 1. Patient clinical characteristics.**

|  | No PIA (n=99) | Unstable PIA (n=175) | Stable PIA (n=31) | *p*-value |
|---|---|---|---|---|
| Age, years | 58±11 | 57±10 | 58±11 | 0.859 |
| Men, n (%) | 78 (78.8) | 120 (68.6) | 25 (80.7) | 0.113 |
| BMI, kg/m$^2$ | 24.69±3.63 | 25.16±3.64 | 25.21±3.31 | 0.569 |
| Time from symptom onset to reperfusion, min | 296±156 | 283±180 | 316±171 | 0.570 |
| STEMI onset upon exertion, n (%) | 80 (80.8) | 101 (57.7) | 21 (67.7) | 0.001 |
| Risk factors, n (%) |  |  |  |  |
| Hypertension | 40 (40.4) | 94 (53.7) | 16 (51.6) | 0.102 |
| Dyslipidaemia | 66 (66.7) | 112 (64.0) | 17 (54.8) | 0.488 |
| Diabetes mellitus | 26 (26.3) | 54 (30.9) | 6 (19.4) | 0.369 |
| Current smoking | 71 (71.7) | 107 (61.1) | 20 (64.5) | 0.212 |
| Family history of CAD | 32 (32.3) | 65 (37.1) | 8 (25.8) | 0.409 |

Laboratory results

| | | | | |
|---|---|---|---|---|
| TC, mg/dL | 187.84±37.65 | 192.97±39.10 | 182.06±36.71 | 0.277 |
| LDL-C, mg/dL | 120.08±35.87 | 124.90±35.39 | 114.80±28.42 | 0.263 |
| HDL-C, mg/dL | 47.96±12.36 | 49.98±10.83 | 49.72±10.71 | 0.372 |
| TG, mg/dL | 167.73±137.00 | 153.03±120.17 | 142.66±86.23 | 0.519 |
| HbA1c, % | 6.28±1.54 | 6.33±1.27 | 6.14±1.46 | 0.804 |
| eGFR, ml/min/1.73 m$^2$ | 92.72±21.62 | 92.63±21.12 | 91.37±23.53 | 0.951 |
| Peak CK-MB (µg/L) | 255.47±223.89 | 202.31±237.63 | 273.14±226.91 | 0.098 |
| Peak TnI, µg/L | 120.90±120.04 | 91.23±106.40 | 118.82±148.33 | 0.095 |

Values are presented as mean±SD or n (%).

BMI: body mass index; CAD: coronary artery disease; CK-MB: creatinine kinase-myocardial band; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PIA: pre-infarction angina; STEMI: ST-segment elevation myocardial infarction; TC: total cholesterol; TG: triglyceride; TnI: troponin I

**Supplementary Table 2. Angiographic findings.**

| | No PIA | Unstable PIA | Stable PIA | *p*-value |
|---|---|---|---|---|
| | (n=99) | (n=175) | (n=31) | |
| Infarct-related artery, n (%) | | | | 0.523 |
|    LAD | 44 (44.4) | 89 (50.9) | 19 (61.3) | |
|    LCX | 12 (12.1) | 16 (9.1) | 3 (9.7) | |
|    RCA | 43 (43.4) | 70 (40.0) | 9 (29.0) | |
| Multivessel disease, n (%) | 49 (49.5) | 96 (54.9) | 17 (54.8) | 0.680 |
| TIMI flow grade at presentation, n (%) | | | | 0.386 |
|    0 | 72 (72.7) | 130 (74.3) | 19 (61.3) | |
|    1 | 4 (4.0) | 3 (1.7) | 2 (6.5) | |
|    2 | 16 (16.2) | 25 (14.3) | 5 (16.1) | |
|    3 | 7 (7.1) | 17 (9.7) | 5 (16.1) | |
| Thrombus aspiration, n (%) | 93 (93.9) | 156 (89.1) | 25 (80.6) | 0.091 |
| TIMI flow grade after thrombus aspiration, n (%) | | | | 0.654 |
|    2 | 27 (27.3) | 54 (30.9) | 11 (35.5) | |
|    3 | 72 (72.7) | 121 (69.1) | 20 (64.5) | |
| QCA analysis at baseline | | | | |
|    MLD, mm | 0.18±0.39 | 0.17±0.36 | 0.17±0.34 | 0.989 |
|    Diameter stenosis, % | 93.51±13.38 | 93.69±12.74 | 92.39±12.35 | 0.875 |
| QCA analysis after thrombus aspiration | | | | |
|    RVD, mm | 2.91±0.82 | 2.81±0.52 | 2.85±0.46 | 0.524 |
|    MLD, mm | 1.15±0.43 | 1.06±0.43 | 1.16±0.51 | 0.204 |
|    Diameter stenosis, % | 57.78±16.74 | 62.26±14.40 | 60.46±15.01 | 0.090 |
|    Lesion length, mm | 12.68±4.56 | 14.17±6.89 | 14.16±8.68 | 0.203 |
| Presence of collaterals, n (%) | 34 (34.3) | 85 (48.6) | 16 (51.6) | 0.051 |

Values are presented as mean±SD or n (%).

LAD: left anterior descending; LCX: left circumflex artery; MLD: minimum lumen diameter; PIA: pre-infarction angina; QCA: quantitative coronary angiography; RCA: right coronary artery; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction

**Supplementary Table 3. OCT qualitative and quantitative findings at the culprit lesion site.**

| | No PIA [a] | Unstable PIA [b] | Stable PIA [c] | p-value | | | |
|---|---|---|---|---|---|---|---|
| | (n=99) | (n=175) | (n=31) | Overall | [a] vs. [b] | [a] vs. [c] | [b] vs. [c] |
| **Qualitative analysis** | | | | | | | |
| Plaque composition, n (%) | | | | 0.525 | | | |
| Fibrous plaque | 9 (9.1) | 24 (3.7) | 4 (2.9) | | | | |
| Lipid-rich plaque | 90 (90.9) | 151 (86.3) | 27 (87.1) | | | | |
| TCFA, n (%) | 80 (80.8) | 112 (64.0) | 17 (54.8) | 0.004 | 0.004* | 0.004* | 0.331 |
| Plaque morphology, n (%) | | | | 0.022 | 0.013* | 0.028 | 0.527 |
| Rupture | 72 (72.7) | 101 (57.7) | 16 (51.6) | | | | |
| IFC | 27 (27.3) | 74 (42.3) | 15 (48.4) | | | | |
| Residual thrombus, n (%) | 92 (92.9) | 162 (92.6) | 28 (90.3) | 0.951 | | | |
| Thrombus type, n (%) | | | | 0.008 | 0.007* | 0.020 | 0.417 |
| White thrombus | 46 (50.0) | 109 (67.3) | 21 (75.0) | | | | |
| Red thrombus | 46 (50.0) | 53 (32.7) | 7 (25.0) | | | | |
| Macrophages, n (%) | 89 (89.9) | 154 (88.0) | 26 (83.9) | 0.657 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cholesterol crystals, n (%) | 41 (41.4) | 79 (45.1) | 11 (35.5) | 0.564 | | | |
| Microchannels, n (%) | 38 (38.4) | 59 (33.7) | 14 (45.2) | 0.419 | | | |
| Calcification, n (%) | 23 (23.2) | 52 (29.7) | 10 (32.3) | 0.438 | | | |
| **Quantitative analysis** | | | | | | | |
| Minimal FCT, μm | 58.0±17.4 | 68.3±27.5 | 75.6±31.8 | 0.001 | 0.007* | 0.005* | 0.526 |
| Maximal lipid arc, ° | 294.07±67.58 | 276.69±66.10 | 262.36±62.35 | 0.047 | 0.151 | 0.097 | 0.930 |
| Maximum ruptured cavity CSA, mm$^2$ | 1.53±1.20 | 1.02±1.09 | 0.82±0.72 | 0.006 | 0.011* | 0.089 | 1.000 |
| Thrombus volume, mm$^3$ | 3.79±5.28 | 2.95±4.01 | 4.02±4.91 | 0.258 | | | |
| Mean reference vessel area, mm$^2$ | 6.97±2.43 | 7.00±2.87 | 7.60±3.12 | 0.498 | | | |
| Minimum lumen area, mm$^2$ | 2.13±1.29 | 1.79±1.01 | 1.88±1.15 | 0.055 | | | |
| Lumen area stenosis, % | 68.34±16.22 | 72.76±12.45 | 73.63±13.00 | 0.027 | 0.035* | 0.204 | 1.000 |

Values are presented as mean±SD or n (%).

* Indicates significance after Bonferroni correction.

CSA: cross-sectional area; FCT: fibrous cap thickness; IFC: intact fibrous cap; OCT: optical coherence tomography; PIA: pre-infarction angina; TCFA: thin-cap fibroatheroma

**Supplementary Table 4. Clinical outcomes at the 1-year follow-up.**

| Variable | Patients with PIA (n=203) | Patients without PIA (n=98) | *p*-value |
|---|---|---|---|
| Follow-up time, months | 13.6±3.6 | 14.3±4.0 | 0.169 |
| MACE, n (%) | 16 (7.9) | 12 (12.2) | 0.222 |
| Cardiac death, n (%) | 4 (2.0) | 1 (1.0) | 0.546 |
| Re-MI, n (%) | 2 (1.0) | 1 (1.0) | 0.977 |
| TLR, n (%) | 8 (3.9) | 7 (7.1) | 0.232 |
| Unstable angina, n (%) | 6 (3.0) | 4 (4.1) | 0.610 |

Values are presented as n (%).

Cardiac death: cardiac death related to the target vessel; MACE: major adverse cardiovascular events (the composite of cardiac death related to the target vessel, recurrent myocardial infarction related to the target vessel, clinically driven target lesion revascularisation, or unstable angina requiring hospitalisation); Re-MI: recurrent myocardial infarction related to the target vessel; TLR: clinically driven target lesion revascularisation; Unstable angina: unstable angina requiring hospitalisation. Other abbreviations are listed in Supplementary Table 3.