

Predictors of non-stenting strategy for acute coronary syndrome caused by plaque erosion: four-year outcomes of the EROSION study

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KEYWORDS

- ACS/NSTE-ACS
- optical coherence tomography
- STEMI

Abstract

Background: The EROSION study demonstrated that patients with an acute coronary syndrome (ACS) caused by plaque erosion could be treated with antithrombotic therapy without stenting. However, the long-term prognosis of this strategy is still unclear.

Aims: The aim of this study was to test whether a non-stenting antithrombotic strategy was still effective at four-year follow-up and to explore potential predictors of long-term prognosis.

Methods: This study was a long-term follow-up of the EROSION study. Follow-up was conducted by phone call or clinical visit. Patients were divided into two groups – those with target lesion revascularisation (the TLR group), and the non-TLR group.

Results: Out of 55 patients who completed one-month follow-up, 52 patients finished four-year follow-up. The median duration was 4.8 years (range, 4.2-5.8 years). The majority of patients remained free from events, and all patients were free from hard endpoints (death, myocardial infarction, stroke, bypass surgery, or heart failure). Only one patient had gastrointestinal bleeding, and 11 patients underwent TLR. Patients in the non-TLR group had more optical coherence tomography (OCT) thrombus reduction from baseline to one month; 95% of patients in the non-TLR group versus 45% in the TLR group ($p=0.001$) met the primary endpoint (thrombus volume reduction $>50\%$). Angiographic results showed that the TLR group had less improvement in diameter stenosis ($p=0.014$) at one month compared with the non-TLR group.

Conclusions: Four-year follow-up findings reconfirmed the safety of an antithrombotic therapy without stenting for ACS caused by erosion. Patients with better response to antithrombotic therapy in the first month were less likely to require stent implantation during the next four years.

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Abbreviations

ACS	acute coronary syndrome
DAPT	dual antiplatelet therapy
MACE	major adverse cardiovascular events
MI	myocardial infarction
OCT	optical coherence tomography
PCI	percutaneous coronary intervention
TIMI	Thrombolysis In Myocardial Infarction
TLR	target lesion revascularisation

Introduction

Early and late stent-related complications (stent thrombosis and stent restenosis) remain challenging problems, especially in patients presenting with acute coronary syndrome (ACS) and undergoing primary percutaneous coronary intervention (PCI) with stent implantation, without taking into consideration differences in underlying mechanisms¹⁻³. Plaque rupture and plaque erosion are the most common causes of ACS, accounting for 60-70% and 30-40% of ACS, respectively⁴. However, plaque erosion differs from plaque rupture because erosions have less lipid and more platelet-rich thrombus, and patients with erosions are more often smokers and female⁵⁻⁷. Because optical coherence tomography (OCT) allows *in vivo* detection of plaque erosion (vs plaque rupture)⁸, we performed a proof-of-concept study entitled EROSION (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in Plaque Erosion) to test the safety and feasibility of not stenting erosion ACS-related culprit lesions. Favourable results were observed at one month and one year^{9,10}. In the current study we report four-year outcomes.

Methods

STUDY DESIGN

This study was a long-term follow-up of the EROSION study. The EROSION study was a single-arm, prospective, proof-of-concept study (NCT02041650); the detailed protocols have been published previously^{9,10}. Briefly, when an ACS patient was diagnosed as having plaque erosion by OCT with <70% residual angiographic diameter stenosis (DS) after thrombus aspiration, Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and no progressive chest pain, the patient was treated with antithrombotic therapy without stenting. Manual aspiration and glycoprotein IIb/IIIa inhibitor (GPI) use were based on clinical practice. The primary endpoint was >50% reduction of thrombus volume measured by OCT at one month. Major adverse cardiovascular events (MACE: a composite of cardiac death, reinfarction, re-hospitalisation due to unstable or progressive angina, clinically driven target lesion revascularisation [TLR], stroke, and major bleeding) were the secondary endpoints.

In the present study, clinical follow-up was carried out either by phone call or by clinical visit every three months in the first year and annually after 12 months. A questionnaire collected detailed information of clinical events during the four years including

MACE, quality of life, and medications. Detailed definitions of each event have been listed in previous papers^{9,10}. Medications included aspirin, ticagrelor/clopidogrel, statins, β -blockers, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB).

A detailed methodology of angiographic and OCT image analysis has been described in previous studies^{9,10}. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Harbin Medical University (Harbin, China). All patients provided written informed consent.

STATISTICAL ANALYSIS

SPSS, Version 25.0 (IBM Corp., Armonk, NY, USA) was used to analyse all data. The Kolmogorov-Smirnov test was used for continuous variables to determine their distribution. An independent samples t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Continuous variables are shown as mean \pm SD for normally distributed variables or median (interquartile range) for non-normally distributed variables. Categorical data are shown as absolute frequencies (percentages) and analysed using the chi-square test or Fisher's exact test. A multivariable logistic regression analysis was conducted to explore independent predictors of TLR. Receiver operating characteristics with area under the curve (AUC) were used to determine the best cut-off value for continuous predictors of TLR. A two-tailed p-value <0.05 was considered statistically significant.

Results

Among 55 EROSION study patients who finished one-month follow-up, 52 patients completed four-year follow-up (median duration of 58 months [4.8 years]) (Figure 1). Two patients were lost

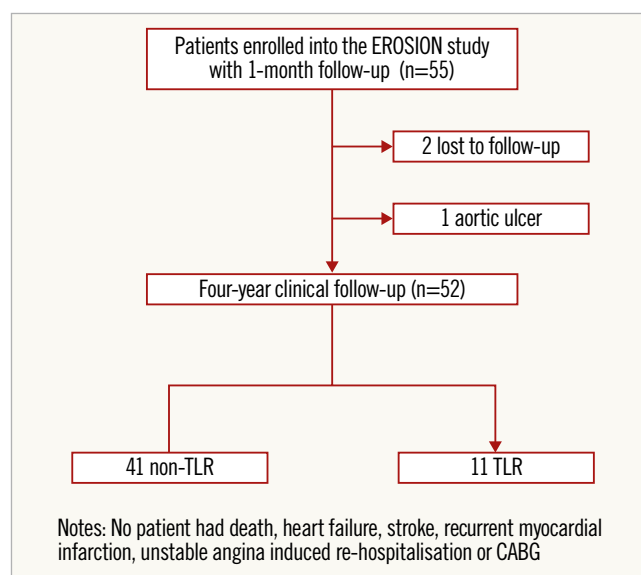


Figure 1. The study flow chart. CABG: coronary artery bypass grafting; TLR: target lesion revascularisation

to follow-up, and one quit the study because a computed tomography (CT) scan confirmed an aortic ulcer at one month. No patient experienced death, stroke, recurrent myocardial infarction (MI), coronary artery bypass grafting (CABG), or heart failure.

At four years, 11 out of 52 patients (21%) underwent elective PCI with stent implantation while the other 41 (79%) remained free from revascularisation. Ten of them underwent revascularisation because of exertional angina, and one patient was stented because of a tight stenosis on angiography at one-month follow-up. Timing and angiographic information for these 11 patients at the time of repeat revascularisation is shown in **Figure 2** and **Supplementary Table 1**. Five patients underwent TLR within one year, and six patients were stented between one and four years.

Details of medications and clinical events at four years are reported in **Supplementary Table 2**. All patients were on dual antiplatelet therapy (DAPT) for at least 12 months, except for one patient who stopped ticagrelor at three months due to gastrointestinal bleeding. At four-year follow-up, 44 of 52 (85%) patients continued to take aspirin, 6 of 52 (12%) continued to receive DAPT, and 34 patients (65%) were on statins with a higher tendency in the TLR group versus the non-TLR group (10 [91%] vs 24 [59%], $p=0.073$).

BASELINE CLINICAL, ANGIOGRAPHIC AND OCT FINDINGS IN PATIENTS WITH VERSUS THOSE WITHOUT TLR DURING FOUR-YEAR FOLLOW-UP

Baseline characteristics of patients with versus those without four-year TLR are shown in **Table 1-Table 3**. TLR patients tended to be older (56.0 ± 9.6 vs 50.3 ± 9.9 years, $p=0.097$) and more were >55 years of age (8 [73%] vs 12 [29%], $p=0.014$). Other cardiovascular risk factors and biomarkers were comparable. Except for a higher post-PCI angiographic DS ($60.3\pm 10.1\%$ vs $54.1\pm 9.7\%$, $p=0.066$) in the TLR group, lesion location and pre-PCI lesion severity were similar between the two groups.

CLINICAL, ANGIOGRAPHIC, AND OCT FINDINGS AT 30 DAYS IN PATIENTS WITH VERSUS THOSE WITHOUT TLR DURING FOUR-YEAR FOLLOW-UP

One-month follow-up data are summarised in **Table 4**, **Table 5**, and **Supplementary Table 3**. After 30 days of antithrombotic treatment, patients in the non-TLR group showed improvement in terms of reduction in the angiographic DS ($10.7\pm 13.3\%$ vs $-0.1\pm 9.1\%$, $p=0.014$) when compared with those in the TLR group, resulting in a smaller DS ($48.2\pm 11.2\%$ vs $60.1\pm 10.4\%$, $p=0.003$) and a larger minimum lumen diameter (1.60 ± 0.55 vs 1.24 ± 0.35 mm, $p=0.044$) at follow-up (**Figure 3**).

Notably, in the four-year non-TLR group compared to the TLR group there was a larger reduction in thrombus volume

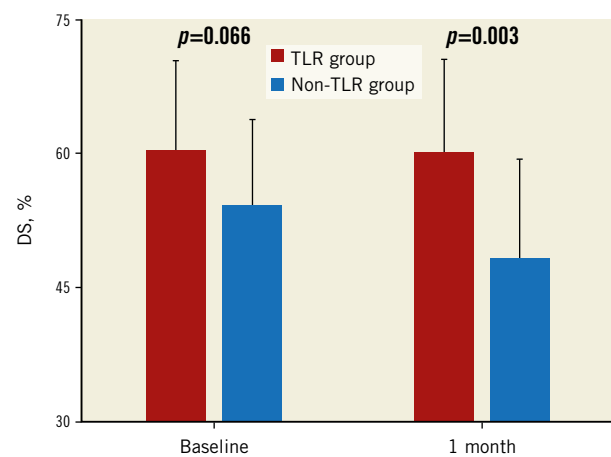


Figure 3. Angiographic DS evolution from baseline to one month. TLR patients had more severe DS at one-month follow-up. There was less lesion regression (DS reduction) in the TLR group after one-month antithrombotic therapy. DS: diameter stenosis; TLR: target lesion revascularisation

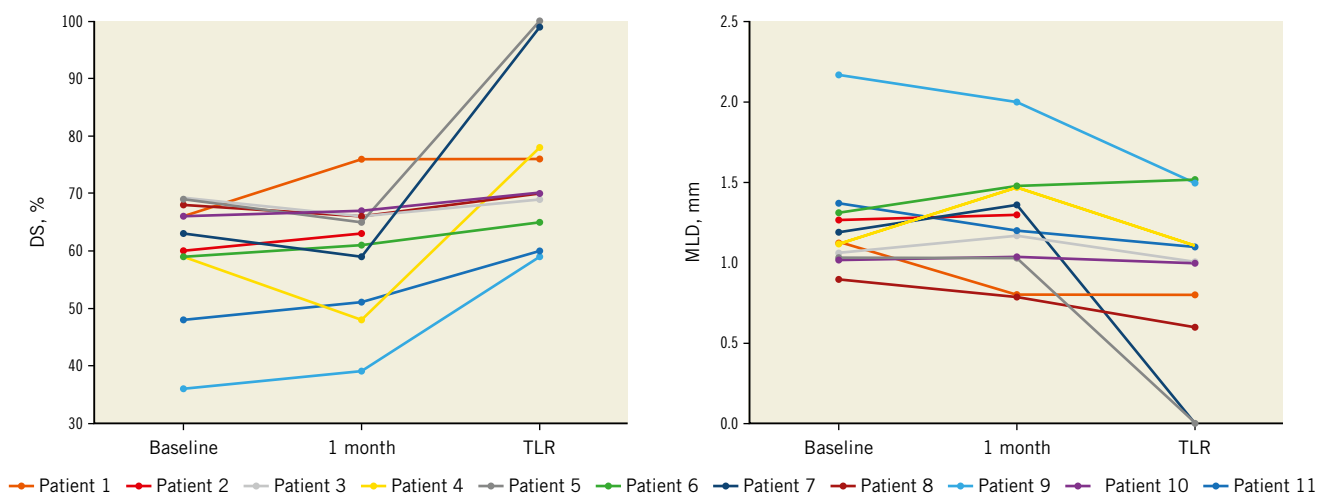


Figure 2. Detailed angiographic progressions of the 11 TLR patients between baseline and revascularisation. DS: diameter stenosis; MLD: minimal lumen diameter; TLR: target lesion revascularisation

Table 1. Baseline clinical characteristics.

		Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	p-value
Clinical characteristics					
Age, years		51.5±10.0	56.0±9.6	50.3±9.9	0.097
Age >55 years		20 (38)	8 (73)	12 (29)	0.014
Male		45 (87)	9 (82)	36 (88)	0.630
Smoking		39 (75)	9 (82)	30 (73)	0.709
Diabetes mellitus		5 (10)	1 (9)	4 (10)	1.000
Hypertension		15 (29)	3 (27)	12 (29)	1.000
Prior PCI		2 (4)	2 (18)	0 (0)	0.041
Clinical presentation	STEMI	50 (96)	10 (91)	40 (98)	0.382
	NSTEMACS	2 (4)	1 (9)	1 (2)	
Laboratory data					
LDL-C, mg/dL		107.9±36.1	121.1±34.7	104.3±36.2	0.196
hs-CRP, mg/L		6.7 (2.2-11.9)	11.3 (5.2-13.3)	5.7 (1.9-11.7)	0.125
Creatinine, µmol/L		76.5±23.9	78.2±30.6	76.0±22.2	0.790
CK-MB, µg/L		12.4 (1.8-58.7)	42.6 (2.4-153.2)	12.3 (1.6-30.1)	0.262
Tnl, µg/L		1.5 (0.1-8.9)	20.3 (0.3-28.4)	1.3 (0.1-6.3)	0.079
Procedure characteristics					
Manual thrombectomy		43 (83)	8 (73)	35 (85)	0.378
GPI		33 (63)	5 (45)	28 (68)	0.181
Values are mean±SD, median (interquartile range) or n (%). CK-MB: creatine kinase myocardial band; GPI: glycoprotein IIb/IIIa inhibitor; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; NSTEMACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; Tnl: troponin I					

Table 2. Baseline angiographic characteristics.

		Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	p-value
Lesion location	LAD	34 (65)	5 (46)	29 (71)	0.106
	LCX	5 (10)	3 (27)	2 (5)	
	RCA	13 (25)	3 (27)	10 (24)	
Pre thrombectomy					
TIMI	0/1	32 (62)	7 (64)	25 (61)	1.000
	2/3	20 (38)	4 (36)	16 (39)	
Post thrombectomy					
MLD, mm		1.39±0.45	1.23±0.34	1.43±0.47	0.204
RVD, mm		3.10±0.58	3.10±0.27	3.10±0.64	0.998
DS, %		55.4±10.0	60.3±10.1	54.1±9.7	0.066
Lesion length, mm		13.0±3.6	12.4±3.1	13.2±3.8	0.533
Values are mean±SD or n (%). DS: diameter stenosis; LAD: left anterior descending artery; LCX: left circumflex artery; MLD: minimal lumen diameter; RCA: right coronary artery; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction					

(94.9 [73.8-100.0] % vs 44.2 [23.9-100.0] %, $p=0.016$), thrombus burden (87.5 [39.7-100.0] % vs 3.0 [-10.5-100.0] %, $p=0.016$), maximum thrombus area (86.4 [37.2-100.0] % vs 9.1 [-4.8-100.0] %, $p=0.016$), and thrombus score (88.8 [72.4-100.0] % vs 35.6 [8.4-100.0] %, $p=0.040$) at one month, indicative of more thrombus dissolution during this initial one-month period. Fewer than 50% of patients who underwent TLR within the four-year follow-up period reached the primary endpoint of the EROSION study (thrombus volume decrease >50% at one month), whereas almost all patients in the non-TLR group achieved this primary endpoint (5 [45%] vs 39 [95%], $p=0.001$)

(**Figure 4**). Representative cases of TLR and non-TLR are shown in **Figure 5** and **Figure 6**.

PREDICTORS OF TLR

According to clinical features, the evolution of angiographic and OCT characteristics during one-month follow-up, and the results of univariate analysis and their mechanistic relationship to TLR, we selected four variables to test in the multivariate analysis – patient age, angiographic DS improvement at one month, thrombus volume reduction at one month, and OCT minimal flow area at one month. There was no correlation (Pearson's correlation,

Table 3. Baseline OCT characteristics.

		Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	p-value
Plaque type	Fibrous	27 (52)	4 (36)	23 (56)	0.317
	Lipid	25 (48)	7 (64)	18 (44)	
Macrophage		19 (37)	5 (45)	14 (34)	0.503
Cholesterol crystals		8 (15)	3 (27)	5 (12)	0.343
Microchannel		17 (33)	6 (55)	11 (27)	0.145
Calcification		12 (23)	4 (36)	8 (20)	0.253
Thrombus type	White	39 (75)	7 (64)	32 (78)	0.435
	Red	13 (25)	4 (36)	9 (22)	
Thrombus volume, mm ³		4.0 (2.0-12.6)	4.9 (2.1-7.4)	3.7 (1.3-13.2)	0.937
Thrombus burden, %		16.3 (9.6-23.9)	16.0 (9.8-25.6)	16.6 (9.2-22.6)	0.762
Mean thrombus area, mm ²		0.5 (0.3-1.1)	0.5 (0.3-1.2)	0.5 (0.3-1.0)	0.937
Max thrombus area, mm ²		1.2 (0.6-2.5)	1.2 (0.9-2.2)	1.2 (0.6-2.6)	0.849
Thrombus length, mm		8.3 (5.8-13.9)	6.4 (5.8-13.6)	8.4 (5.8-14.5)	0.538
Thrombus score		54.5 (39.0-92.8)	54.0 (40.0-83.0)	55.0 (39.0-97.5)	0.902
Minimal flow area, mm ²		1.6 (1.4-2.7)	1.6 (1.4-2.3)	1.7 (1.3-2.9)	0.762
Values are median (interquartile range) or n (%).					

Table 4. One-month angiographic findings.

		Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	p-value
TIMI	0/1	0 (0)	0 (0)	0 (0)	1.000
	2/3	52 (100)	11 (100)	41 (100)	
MLD, mm		1.53±0.53	1.24±0.35	1.60±0.55	0.044
RVD, mm		3.11±0.68	3.12±0.45	3.10±0.73	0.956
DS, %		50.8±11.9	60.1±10.4	48.2±11.2	0.003
DS <50%, n (%)		24 (46.2)	2 (18.2)	22 (53.7)	0.046
Lesion length, mm		13.0±3.2	12.6±2.9	13.1±3.3	0.659
Reduction of DS, %		8.4±13.2	-0.1±9.1	10.7±13.3	0.014
Values are mean±SD or n (%). DS: diameter stenosis; MLD: minimal lumen diameter; RVD: reference vessel diameter; TIMI: Thrombolysis In Myocardial Infarction					

Table 5. One-month OCT findings.

		Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	p-value
Thrombus type	White	28 (54)	5 (46)	23 (56)	-
	Red	4 (8)	3 (27)	1 (2)	
	No thrombus	20 (38)	3 (27)	17 (42)	
Thrombus volume, mm ³		0.3 (0.0-2.5)	4.2 (0.0-5.6)	0.2 (0.0-1.9)	0.065
Thrombus burden, %		3.7 (0.0-10.1)	13.8 (0.0-25.6)	2.8 (0.0-7.5)	0.030
Mean thrombus area, mm ²		0.2 (0.0-0.5)	0.4 (0.0-1.1)	0.1 (0.0-0.4)	0.092
Max thrombus area, mm ²		0.3 (0.0-1.1)	0.8 (0.0-2.5)	0.2 (0.0-0.8)	0.062
Thrombus length, mm		1.9 (0.0-5.1)	2.8 (0.0-10.8)	1.5 (0.0-4.8)	0.181
Thrombus score		8.5 (0.0-27.8)	29.0 (0.0-76.0)	7.0 (0.0-22.5)	0.088
Minimal flow area, mm ²		2.1 (1.5-3.8)	1.8 (1.1-2.7)	2.2 (1.6-4.1)	0.049
Reduction of thrombus (%)					
Thrombus volume, %		94.0 (60.3-100.0)	44.2 (23.9-100.0)	94.9 (73.8-100.0)	0.016
Thrombus burden, %		83.1 (9.3-100.0)	3.0 (-10.5-100.0)	87.5 (39.7-100.0)	0.016
Mean thrombus area, %		82.1 (14.6-100.0)	3.1 (0.1-100.0)	84.6 (26.6-100.0)	0.072
Max thrombus area, %		81.9 (22.3-100.0)	9.1 (-4.8-100.0)	86.4 (37.2-100.0)	0.016
Thrombus length, %		77.8 (54.2-100.0)	38.7 (14.4-100.0)	82.7 (61.9-100.0)	0.080
Thrombus score, %		87.4 (58.9-100.0)	35.6 (8.4-100.0)	88.8 (72.4-100.0)	0.040
Minimal flow area, %		-14.1 (-42.3-9.7)	6.2 (-15.5-27.3)	-17.4 (-48.8-7.3)	0.034
Values are median (interquartile range) or n (%).					

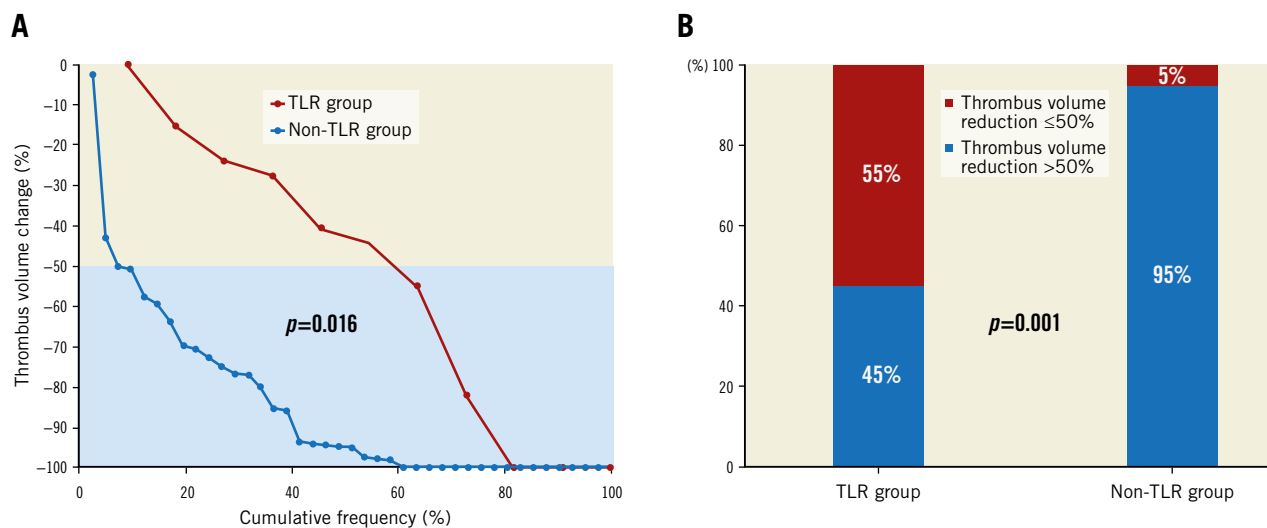


Figure 4. Thrombus reduction after one-month effective antithrombotic therapy in the TLR versus the non-TLR group. A) Individual thrombus volume evolution in the TLR versus the non-TLR group. B) Percentage of thrombus volume decrease >50% in the TLR versus the non-TLR group. TLR: target lesion revascularisation

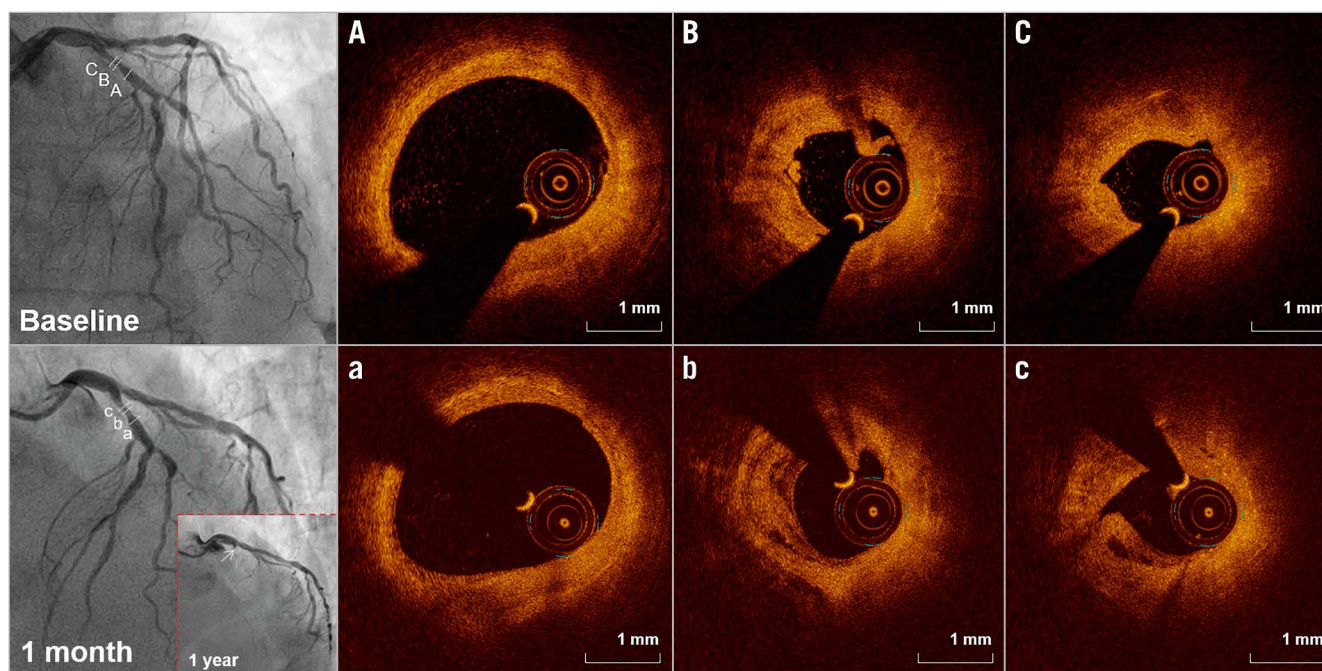


Figure 5. Representative case with target lesion revascularisation. A 69-year-old female without cardiovascular risk factors presented with STEMI with a 65% angiographic stenosis in the LAD after manual thrombectomy (upper left). OCT showed plaque erosion in the culprit site (A-C). After one-month antithrombotic therapy, there was no improvement on the angiogram (lower left) and no thrombus reduction on the OCT images (a-c). The patient had angina at one-year follow-up and the angiogram showed total occlusion (white arrow). Stent implantation was performed. LAD: left anterior descending artery; OCT: optical coherence tomography; STEMI: ST-segment elevation myocardial infarction

$p < 0.01$) among any of these variables. Thrombus volume reduction at one month was the only independent predictor of TLR during four years of follow-up (odds ratio [OR], 0.97) (**Supplementary Table 4**). Using receiver operating curves, the best cut-off value of one-month thrombus volume reduction to predict TLR was 56.2% (AUC: 0.731, Youden's index: 0.539, sensitivity: 0.902,

specificity: 0.636, $p = 0.020$), very close to the primary endpoint of the EROSION study.

Discussion

In the current study we report the long-term outcomes of ACS patients with OCT-detected culprit lesion plaque erosion who

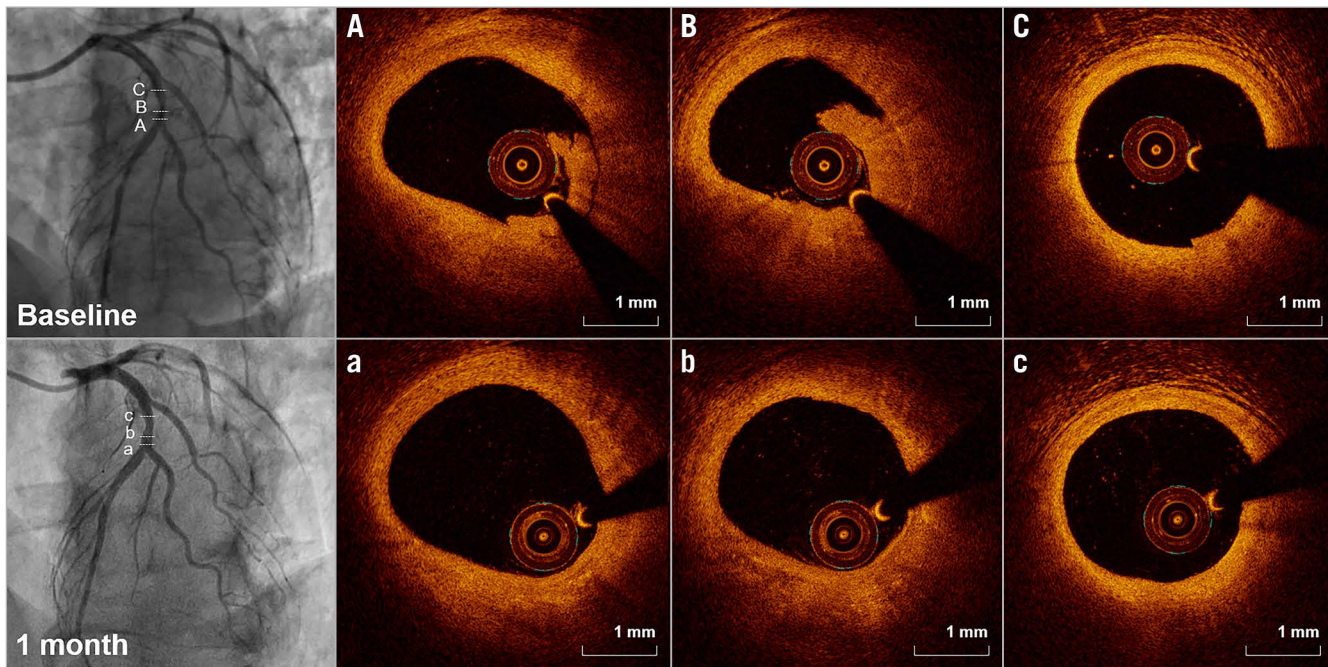


Figure 6. Representative case without target lesion revascularisation. A 56-year-old male without cardiovascular risk factors presented with STEMI with a 50% angiographic stenosis in the LAD after manual thrombectomy (upper left). Plaque erosion was detected by OCT (A-C). After one-month antithrombotic therapy, there was a significant improvement in the angiogram (lower left) and no residual thrombus on OCT images (a-c). The patient remained well at a five-year follow-up. LAD: left anterior descending artery; OCT: optical coherence tomography; STEMI: ST-segment elevation myocardial infarction

were treated without stent implantation during the primary PCI. The main findings of this study are as follows. (1) The majority of patients remained free from events (and all patients were free from hard events such as death, stroke, recurrent MI, CABG, or heart failure) at a median follow-up time of 58 months, reconfirming the feasibility and safety of a non-stenting strategy for patients with ACS caused by erosion. (2) The overall TLR rate was 21% at four-year follow-up. (3) Patients who improved from baseline to one month (based on OCT assessment of thrombus burden) were the ones who did well at four (or more) years of follow-up.

COMPREHENSIVE EVALUATION OF THE EROSION STUDY

Previous studies, as well as the one-month and one-year results of the EROSION study, suggested that ACS patients with an intact culprit lesion fibrous cap or an OCT-detected culprit erosion did better than patients with culprit lesion plaque rupture and could be treated without stent implantation during the primary PCI⁹⁻¹⁴. However, the long-term (beyond one year) safety of this strategy and, in particular, the rate of recurrent MI was not addressed. The cumulative rate of MACE and TLR in the current study was 23% (12 of 52) and 21% (11 of 52), respectively, with a median follow-up time of five years. MACE were primarily related to TLR in the current study, except for one patient with gastrointestinal bleeding at three months. In particular, all TLR in the present study were non-emergent and not associated with an ACS.

INSIGHTS ON POTENTIAL MECHANISMS OF TLR

Based on the angiographic findings that patients who underwent revascularisation showed significant progression with greater severity of stenosis and smaller luminal diameter compared to baseline, organisation of residual thrombus probably contributed to lesion progression. This was also supported by OCT findings that thrombus volume reduction at one month was significantly smaller in patients with TLR versus those without TLR. Considering previous studies and the angiographic findings during revascularisation, we speculated that the possible mechanisms of TLR in the current erosion patients treated conservatively were insufficient dissolution of residual thrombus and the formation of new thrombus during the process of residual thrombus organisation, leading to lesion progression^{4,15}. Different from the rapid and massive thrombosis in the acute setting of MI, this might be a chronic and repeated process of thrombosis followed by organisation.

The underlying mechanism for insufficient thrombus dissolution might be the poor response to antithrombotic treatment, which is affected by several factors such as age, race, genetic polymorphism, etc.¹⁶. There is a relationship between high platelet reactivity (HPR) and ischaemic events¹⁷, although the feasibility of HPR to predict clinical outcomes is still controversial^{18,19}. Besides, the emergence of new P2Y₁₂ inhibitors has provided increased benefits, especially in ACS patients. In the current study, all patients took a new P2Y₁₂ inhibitor (ticagrelor) for at least one year.

CLINICAL IMPLICATIONS

The current study results highlight the importance of responsiveness to antithrombotic therapy in erosion patients treated with a non-stenting strategy, particularly during the first month. Patients with the greatest thrombus dissolution at one month were less likely to require revascularisation at long-term follow-up. While procedural OCT is necessary to identify patients with a culprit lesion erosion, one-month OCT in all such patients is not feasible. Thus, further study should focus on the use of non-invasive methods (such as coronary CT angiography) to identify high-TLR-risk individuals in whom more intensive (or longer-term) medical treatment may be needed. Also, biomarkers should be collected and tested for their ability to identify high-TLR-risk patients. Nevertheless, it is reassuring that, even without a one-month imaging assessment, a non-stenting strategy in these patients may not be associated with an increased frequency of death, MI, stroke, CABG, or heart failure. Conversely, recent studies have focused on high bleeding risk patients as well as on the bleeding complications with long-term dual antiplatelet therapy. Only one patient in the current study had bleeding.

Limitations

First, this study enrolled a relatively small number of patients. Second, two patients who finished one-month follow-up were missed because they could not be contacted. Third, the use of GPI and thrombectomy was decided by the operators. While the latter might have affected lesion morphologies, care was taken to avoid excessive trauma. Fourth, the EROSION study predominantly enrolled young males with a high prevalence of smoking. Fifth, there was no functional evaluation at the time of repeat revascularisation. Sixth, the overlying thrombus might have reduced the accuracy of OCT to assess underlying plaque characteristics. To minimise this limitation, manual thrombus aspiration was performed to remove the thrombus before OCT imaging; patients with residual massive thrombus or an unclassified culprit lesion were excluded from the study. Finally, we do not have long-term OCT data in these patients to assess the degree of ongoing thrombus dissolution.

Conclusions

Four-year follow-up demonstrated that most patients with culprit lesion erosion treated with antithrombotic therapy without stenting in the EROSION study had favourable long-term clinical prognosis, with a cumulative TLR rate of 21%. Patients with poor response to antithrombotic therapy in the first month were more likely to require stent implantation during the next four years.

Impact on daily practice

A mechanism-based strategy should be conducted for ACS patients. Effective antithrombotic therapy without stenting was promising for the majority of ACS patients with underlying plaque erosion. Patients with more effective thrombus dissolution during the first month were more likely to achieve good prognosis and be free from revascularisation at long-term follow-up.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Crea F, Libby P. Acute Coronary Syndromes: The Way Forward From Mechanisms to Precision Treatment. *Circulation*. 2017;136:1155-66.
3. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. *Eur Heart J*. 2015;36:3320-31.
4. Souteyrand G, Arbustini E, Motreff P, Gatto L, Di Vito L, Marco V, Amabile N, Chisari A, Kodama T, Romagnoli E, Tavazzi L, Crea F, Narula J, Prati F. Serial optical coherence tomography imaging of ACS-causing culprit plaques. *EuroIntervention*. 2015;11:319-24.
5. Partida RA, Libby P, Crea F, Jang IK. Plaque erosion: a new in vivo diagnosis and a potential major shift in the management of patients with acute coronary syndromes. *Eur Heart J*. 2018;39:2070-6.
6. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, Kato K, Yonetsu T, Vergallo R, Hu S, Tian J, Lee H, Park SJ, Jang YS, Raffel OC, Mizuno K, Uemura S, Itoh T, Kakuta T, Choi SY, Dauerman HL, Prasad A, Toma C, McNulty I, Zhang S, Yu B, Fuster V, Narula J, Virmani R, Jang IK. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. *J Am Coll Cardiol*. 2013;62:1748-58.
7. Dai J, Xing L, Jia H, Zhu Y, Zhang S, Hu S, Lin L, Ma L, Liu H, Xu M, Ren X, Yu H, Li L, Zou Y, Zhang S, Mintz GS, Hou J, Yu B. In vivo predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study. *Eur Heart J*. 2018;39:2077-85.
8. Mintz GS, Guagliumi G. Intravascular imaging in coronary artery disease. *Lancet*. 2017;390:793-809.
9. Jia H, Dai J, Hou J, Xing L, Ma L, Liu H, Xu M, Yao Y, Hu S, Yamamoto E, Lee H, Zhang S, Yu B, Jang IK. Effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion (the EROSION study). *Eur Heart J*. 2017;38:792-800.
10. Xing L, Yamamoto E, Sugiyama T, Jia H, Ma L, Hu S, Wang C, Zhu Y, Li L, Xu M, Liu H, Bryniarski K, Hou J, Zhang S, Lee H, Yu B, Jang IK. EROSION Study (Effective Anti-Thrombotic Therapy Without Stenting: Intravascular Optical Coherence Tomography-Based Management in Plaque Erosion): A 1-Year Follow-Up Report. *Circ Cardiovasc Interv*. 2017;10:e005860.
11. Tanaka A, Shimada K, Sano T, Namba M, Sakamoto T, Nishida Y, Kawarabayashi T, Fukuda D, Yoshikawa J. Multiple plaque rupture and C-reactive protein in acute myocardial infarction. *J Am Coll Cardiol*. 2005;45:1594-9.
12. Prati F, Uemura S, Souteyrand G, Virmani R, Motreff P, Di Vito L, Biondi-Zoccai G, Halperin J, Fuster V, Ozaki Y, Narula J. OCT-based diagnosis and management of STEMI associated with intact fibrous cap. *JACC Cardiovasc Imaging*. 2013;6:283-7.
13. Niccoli G, Montone RA, Di Vito L, Gramegna M, Refaat H, Scalone G, Leone AM, Trani C, Burzotta F, Porto I, Aurigemma C, Prati F, Crea F. Plaque rupture and intact fibrous cap assessed by optical coherence tomography portend different outcomes in patients with acute coronary syndrome. *Eur Heart J*. 2015;36:1377-84.
14. Yonetsu T, Lee T, Murai T, Suzuki M, Matsumura A, Hashimoto Y, Kakuta T. Plaque morphologies and the clinical prognosis of acute coronary syndrome caused by lesions with intact fibrous cap diagnosed by optical coherence tomography. *Int J Cardiol*. 2016;203:766-74.
15. Wang C, Hu S, Wu J, Yu H, Pan W, Qin Y, He L, Li L, Hou J, Zhang S, Jia H, Yu B. Characteristics and significance of healed plaques in patients with acute coronary

syndrome and stable angina: an in vivo OCT and IVUS study. *EuroIntervention*. 2019;15:e771-8.

16. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol*. 2014;11:597-606.

17. Bonello L, Tantry US, Marcucci R, Blindt R, Angiolillo DJ, Becker R, Bhatt DL, Cattaneo M, Collet JP, Cuisset T, Gachet C, Montalescot G, Jennings LK, Kereiakes D, Sibbing D, Trenk D, Van Werkum JW, Paganelli F, Price MJ, Waksman R, Gurbel PA; Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56:919-33.

18. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, Stone GW, Curzen N, Geisler T, Ten Berg J, Kirtane A, Siller-Matula J, Mahla E, Becker RC, Bhatt DL, Waksman R, Rao SV, Alexopoulos D, Marcucci R, Reny JL, Trenk D, Sibbing D, Gurbel PA; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol*. 2013;62:2261-73.

19. Gurbel PA, Erlinge D, Ohman EM, Neely B, Neely M, Goodman SG, Huber K, Chan MY, Cornel JH, Brown E, Zhou C, Jakubowski JA, White HD, Fox KA, Prabhakaran D, Armstrong PW, Tantry US, Roe MT; TRILOGY ACS Platelet Function

Substudy Investigators. Platelet function during extended prasugrel and clopidogrel therapy for patients with ACS treated without revascularization: the TRILOGY ACS platelet function substudy. *JAMA*. 2012;308:1785-94.

Supplementary data

Supplementary Table 1. Detailed angiographic data of the 11 TLR patients before revascularisation.

Supplementary Table 2. Time durations and medications at four-year follow-up.

Supplementary Table 3. One-month clinical characteristics.

Supplementary Table 4. Univariate and multivariate analysis of TLR.

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Supplementary data

Supplementary Table 1. Detailed angiographic data of the 11 TLR patients before revascularisation.

	TLR time interval, months	Diameter stenosis, %	MLD, mm	Lesion length, mm
Patient 1	1.2	76	0.80	10.39
Patient 2*	-	-	-	-
Patient 3	11.8	69	1.01	10.70
Patient 4	11.8	78	1.10	10.00
Patient 5	11.9	100	-	-
Patient 6	15.2	65	1.52	14.90
Patient 7	17.9	99	-	-
Patient 8	22.8	70	0.60	10.90
Patient 9	25.6	59	1.50	16.00
Patient 10	30.2	70	1.00	12.80
Patient 11	34.2	60	1.10	9.60

*Patient 2 underwent selective PCI in another hospital because of exertional angina after 4 months of antithrombotic therapy.

MLD: minimal lumen diameter; TLR: target lesion revascularisation

Supplementary Table 2. Time durations and medications at four-year follow-up.

	Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	<i>p</i>-value
Time duration, months	58.0 (52.3-60.0)	58.0 (51.0-61.0)	58.0 (52.5-60.0)	0.937
Aspirin	44 (85)	10 (91)	34 (83)	1.000
Ticagrelor or clopidogrel	6 (12)	2 (18)	4 (10)	0.595
DAPT	6 (12)	2 (18)	4 (10)	0.595
Statins	34 (65)	10 (91)	24 (59)	0.073
β -blockers	12 (23)	2 (18)	10 (24)	1.000
ACEI or ARB	2 (4)	0 (0)	2 (5)	1.000

Values are median (interquartile range) or n (%).

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; DAPT: dual antiplatelet therapy; TLR: target lesion revascularisation

Supplementary Table 3. One-month clinical characteristics.

	Overall (n=52)	TLR (n=11)	Non-TLR (n=41)	<i>p</i>-value
LDL-C, mg/dL	70.4 (60.8-96.0)	79.7 (69.7-96.0)	66.6 (58.1-94.9)	0.267
hs-CRP, mg/L	1.1 (0.3-3.7)	1.8 (0.8-5.9)	0.8 (0.3-2.9)	0.111
Creatinine, μ mol/L	71.8 \pm 15.0	68.3 \pm 25.1	72.7 \pm 11.2	0.581
CK-MB, μ g/L	0.6 (0.5-0.9)	0.8 (0.6-1.0)	0.6 (0.4-0.9)	0.142
TnI, μ g/L	0.01 (0.00-0.02)	0.01 (0.00-0.05)	0.01 (0.00-0.02)	0.315

Values are mean \pm SD or median (interquartile range).

CK-MB: creatine kinase myocardial band; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; TLR: target lesion revascularisation; TnI: troponin I

Supplementary Table 4. Univariate and multivariate analysis of TLR.

	Unadjusted			Adjusted		
	OR	95% CI	<i>p</i> -value	OR	95% CI	<i>p</i> -value
Age	1.06	0.99-1.15	0.102	1.06	0.96-1.17	0.250
Angiographic DS reduction at one month	0.91	0.84-0.99	0.020	0.94	0.87-1.03	0.183
Thrombus volume reduction at one month	0.96	0.94-0.99	0.004	0.97	0.94-1.00	0.038
OCT minimal flow area at one month	0.54	0.27-1.08	0.081	0.65	0.30-1.44	0.289

DS: diameter stenosis; OCT: optical coherence tomography; TLR: target lesion
revascularisation