ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–10
doi:10.1093/eurheartj/ehy101

CLINICAL RESEARCH
Acute Coronary Syndromes

In vivo predictors of plaque erosion in patients with ST-segment elevation myocardial infarction: a clinical, angiographical, and intravascular optical coherence tomography study

Jiannan Dai[1,2†], Lei Xing[1,2†], Haibo Jia[1,2†], Yinchun Zhu[1,2], Shaotao Zhang[1,2], Sining Hu[1,2], Lin Lin[1,2], Lijia Ma[1,2], Huimin Liu[1,2], Maoen Xu[1,2], Xuefeng Ren[1,2], Huai Yu[1,2], Lulu Li[1,2], Yanan Zou[1,2], Shaosong Zhang[1,2], Gary S. Mintz[3], Jingbo Hou[1,2]*, and Bo Yu[1,2]*

[1]Department of Cardiology, The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China; [2]The Key Laboratory of Myocardial Ischemia, Chinese Ministry of Education, 246 Xuefu Road, Nangang District, 150086 Harbin, China; and [3]Cardiovascular Research Foundation, New York, 10019 NY, USA

Received 6 October 2017; revised 28 November 2017; editorial decision 14 February 2018; accepted 17 February 2018

Aims Plaque erosion is a significant substrate of acute coronary thrombosis. This study sought to determine *in vivo* predictors of plaque erosion in patients with ST-segment elevation myocardial infarction (STEMI).

Methods and results A prospective series of 822 STEMI patients underwent pre-intervention optical coherence tomography. Using established diagnostic criteria, 209 had plaque erosion (25.4%) and 564 had plaque rupture (68.6%). Plaque erosion was more frequent in women <50 years when compared with those ≥50 years of age ($P = 0.009$). There was a similar, but less striking, trend in men ($P = 0.011$). Patients with plaque erosion were more frequently current smokers but had fewer other coronary risk factors (dyslipidaemia, hypertension, chronic kidney disease, and diabetes mellitus) than those with plaque rupture. There was a preponderance of plaque erosion in the left anterior descending artery (LAD; 61.2%), whereas plaque rupture was more equally distributed in both the LAD (47.0%) and right coronary artery (43.3%). Despite the similar spatial distribution of erosions and ruptures over the lengths of the coronary arteries, plaque erosion occurred more frequently near a bifurcation ($P < 0.001$). In the multivariable analysis, age <50 years, current smoking, absence of other coronary risk factors, lack of multi-vessel disease, reduced lesion severity, larger vessel size, and nearby bifurcation were significantly associated with plaque erosion. Nearby bifurcation and current smoking were especially notable in men, while age <50 years was most predictive in women.

Conclusions Plaque erosion was a predictable clinical entity distinct from plaque rupture in STEMI patients, and gender-specific role of risk factors in plaque erosion should be considered.

Keywords Predictors • Plaque erosion • Plaque rupture • Optical coherence tomography • ST-segment elevation myocardial infarction

* Corresponding author. Tel: +86 451 8660 5180, Fax: +86 451 8660 5180, Email: jingbohou@163.com; Tel: +86 451 8660 5359, Fax: +86 451 8660 5180, Email: yubodr@163.com

† The first 3 authors contributed equally to this article.

Introduction

Rupture of a coronary plaque with a thin fibrous cap has received much attention as a cause of acute coronary syndrome (ACS). However, autopsy and intravascular optical coherence tomography (OCT) studies highlight that a significant portion (~20–40%) of ACS is caused by plaque erosion.[1–4] In stark contrast with plaque rupture, thrombus associated with plaque erosion generally overlies eccentric intact plaques rich in smooth muscle cells and proteoglycans, with superficial endothelial denudation.[1,4–6] Recently, the enticing concept that we might tailor the management strategy of ACS depending on the underlying pathology was tested. In the EROSION study,[7] patients with ST-segment elevation myocardial infarction (STEMI) caused by plaque erosion did not receive coronary artery stent deployment, the current standard of care for STEMI[8] but received intensive antithrombotic treatment. The pilot study demonstrated that most of the subjects had substantial resolution of the intracoronary thrombus after 1 month of follow-up.

Research has made considerable inroads into understanding the pathophysiological basis of plaque rupture. However, the *in vivo* determinants involved in plaque erosion remain largely unknown, including gender-based differences. Better understanding of plaque erosion in clinical setting may inform the development and deployment of novel therapies to combat the residual atherothrombotic risk in the current era.[9,10] Therefore, the present study aims to investigate the predictors of plaque erosion in a large prospective series of STEMI patients, overall as well as in men and women.

Methods

Study design and patients

Patients (aged ≥18 years) presenting with ACS and undergoing emergency procedures were prospectively screened for OCT examination at the 2nd Affiliated Hospital of Harbin Medical University. The main exclusion criteria were cardiogenic shock, end-stage renal disease, serious liver dysfunction, allergy to contrast media, and contraindication to aspirin or ticagrelor. Patients with left main disease, chronic total occlusion, or extremely tortuous or heavily calcified vessels were not included because of the potential difficulty in performing OCT in such situations. Between August 2014 and December 2016, a series of 1008 eligible patients with ACS underwent OCT examination of the culprit lesion; 60 patients with subcritical obstructive plaque erosion from the first 458 patients have already been reported in the EROSION study.[7] Because only 75 patients with non-ST-segment elevation (NSTE)-ACS presented for emergency procedures in our centre, only STEMI patients ($n = 933$) were included in the present study. The study flow chart is shown in *Figure 1*. The definition of STEMI and identification of the culprit lesion were described previously.[7]

The study was approved by the Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University (Harbin, China), and all patients provided written informed consent.

For coronary risk factors and laboratory parameters, see Supplementary material online.

For coronary angiography and analysis, see Supplementary material online.

Optical coherence tomography image acquisition and analysis

A commercially available C7-XR OCT intravascular imaging system (OCT C7 Dragonfly, St. Jude Medical, St Paul, MN, USA) was used in this study. Based on established OCT diagnostic criteria,[2] plaque erosion was identified by the presence of the attached thrombus overlying an intact and visualized plaque, luminal surface irregularity at the culprit lesion in the absence of thrombus, or attenuation of the underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus (Supplementary material online, *Figure S1A–D*). Plaque rupture was identified by the presence of fibrous cap discontinuity with a cavity formed inside the plaque (Supplementary material online, *Figure S1a–d*).

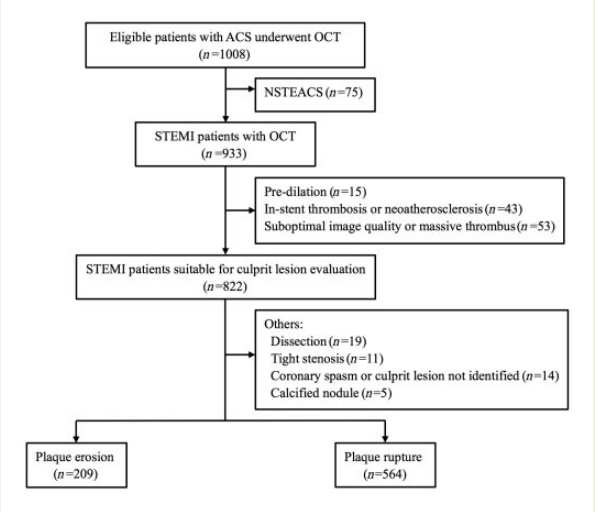


Figure 1 Study flow chart. ACS, acute coronary syndrome; NSTEACS, non-ST-segment elevation acute coronary syndrome; OCT, optical coherence tomography; STEMI, ST-segment elevation myocardial infarction.

The inter-observer kappa coefficients for plaque erosion and plaque rupture were 0.865 and 0.871, respectively. The intra-observer kappa coefficients for plaque erosion and plaque rupture were 0.893 and 0.915, respectively.

Quantitative and qualitative analyses of underlying plaques were performed as described in the Supplementary material online. Nearby bifurcation was pre-defined as erosion or rupture located within 5 mm proximal or distal to a side branch with an orifice diameter >1.0 mm measured by OCT. For plaque erosion, minimal lumen area (MLA) site was chosen for the measurement of the distance between erosion and the nearby bifurcation.[1,11] The site with maximal ruptured cavity was chosen for distance between the plaque rupture and the nearby bifurcation.

Statistical analysis

Statistical analysis was performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and the R. Data distribution was assessed according to the Kolmogorov–Smirnov test. Continuous variables were shown as mean ± standard deviation for normally distributed data or as median (25th–75th percentiles) for non-normally distributed data. Between-group differences were tested using an independent sample *t*-test or the Mann-Whitney *U* test. Categorical data were presented as counts (proportions) and were compared using the χ^2 test or Fisher's exact test. Age <50 years was considered a categorical variable as an indicator for premenopausal status and has been the cut-off used in previous studies.[12,13] The association between plaque erosion and clinical, angiographical, and anatomical characteristics was assessed using a multivariable logistic

Table 1 Baseline characteristics

Variables	Overall (*n* = 773)	Plaque erosion (*n* = 209)	Plaque rupture (*n* = 564)	*P*-value
Age (years)	57.7 ± 10.7	54.6 ± 10.6	58.8 ± 10.4	<0.001
Age <50 years	175 (22.6)	69 (33.0)	106 (18.8)	<0.001
Men	558 (72.2)	165 (78.9)	393 (69.7)	0.011
Coronary risk factors				
Cigarette smoking				0.017
Current smoker	427 (55.2)	133 (63.6)	294 (52.1)	
Former smoker	82 (10.6)	18 (8.6)	64 (11.3)	
Non-smoker	264 (34.2)	58 (27.8)	206 (36.5)	
Diabetes mellitus	156 (20.2)	24 (11.5)	132 (23.4)	<0.001
Hypertension	351 (45.4)	65 (31.1)	286 (50.7)	<0.001
Dyslipidaemia	502 (64.9)	104 (49.8)	398 (70.6)	<0.001
CKD	73 (9.4)	10 (4.8)	63 (11.2)	0.007
Previous history				
Previous MI	18 (2.3)	4 (1.9)	14 (2.5)	0.792
Previous PCI	15 (1.9)	3 (1.4)	12 (2.1)	0.770
Laboratory data				
TC (mg/dL)	185.9 ± 43.4	179.9 ± 46.7	188.1 ± 42.0	0.021
Triglyceride (mg/dL)	135.1 (96.6–170.8)	127.6 (85.5–157.7)	140.8 (100.9–178.9)	<0.001
LDL-C (mg/dL)	123.8 ± 38.9	118.6 ± 44.4	125.7 ± 36.5	0.024
HDL-C (mg/dL)	49.5 ± 12.7	50.6 ± 11.8	49.0 ± 12.9	0.134
TC/HDL-C ratio	3.9 ± 1.2	3.7 ± 1.4	4.0 ± 1.2	0.007
hs-CRP (mg/L)	6.2 (2.3–12.6)	5.4 (1.9–12.6)	6.3 (2.5–12.6)	0.392
Procedural characteristics				
Pre-hospital fibrinolysis	41 (5.3)	11 (5.3)	30 (5.3)	0.975
DAPT to procedure (min)	39.0 (31.0–52.0)	39.0 (30.3–53.0)	40.0 (31.0–51.3)	0.933
Total ischaemic time (h)	4.7 (3.0–8.6)	5.0 (3.4–8.7)	4.7 (2.8–8.5)	0.181

Values are presented as *n* (%), mean ± SD, or median (25th–75th percentiles).
CKD, chronic kidney disease; DAPT, dual anti-platelet therapy; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; TC, total cholesterol.

regression model (with a stepwise selection) based on the results presented in *Tables 1 to 3*. The variables exhibiting a *P*-value <0.1 in the univariate analysis were tested in the multivariable model. The predictive performance of the established model was assessed via Harrell's *c*-index, which was corrected for 'optimism' through bootstrap estimation with 200 replications. Inter- and intra-observer reliability was assessed by kappa statistics. A two-tailed *P*-value <0.05 was considered statistically significant.

Results

Prevalence of plaque erosion

Of the 933 STEMI patients with OCT images, 111 patients were excluded for the following reasons: pre-dilation ($n = 15$), in-stent thrombosis or neoatherosclerosis ($n = 43$), and suboptimal image quality or massive thrombus ($n = 53$). The remaining 822 STEMI patients were suitable for evaluating the culprit lesion. Among them, plaque erosion was identified in 209 (25.4%) patients and plaque rupture in 564 (68.6%) patients. The baseline characteristics of the entire STEMI cohort are presented in Supplementary material, *Table S1*.

Age and gender differences

The baseline characteristics of patients with plaque erosion and plaque rupture are presented in *Table 1*. Patients with plaque erosion were significantly younger than those with plaque rupture ($P < 0.001$). Specifically, patients <50 years of age were more frequent in the erosion group vs. the rupture group ($P < 0.001$). After stratification for age and gender (*Figure 2*), the prevalence of plaque erosion was highest in women <50 years of age and decreased significantly in women ≥50 years of age (47.1% vs. 17.4%, $P = 0.009$). A similar, but less marked, difference was also observed in men (35.3% vs. 24.5%, $P = 0.011$).

Coronary risk factors and laboratory data

Coronary risk factors and laboratory data are presented in *Table 1*. Patients with plaque erosion were more frequently current smokers than those with plaque rupture (63.6% vs. 52.1%, $P = 0.017$). Other coronary risk factors, including diabetes mellitus, hypertension, dyslipidaemia, and chronic kidney disease (CKD) were less common in erosion vs. rupture. Similarly, laboratory data showed that patients

with plaque erosion had lower total cholesterol (TC), triglyceride, low-density lipoprotein cholesterol (LDL-C) levels, and a lower ratio of TC to high-density lipoprotein cholesterol (HDL-C). Serum high-sensitive C-reactive protein (hs-CRP) level, white blood cell and neutrophil counts were comparable between the erosion and rupture groups (*Table 1* and Supplementary material online, *Table S2*).

Angiographical findings

The angiographical findings are presented in *Table 2*. Plaque erosion was most frequently located in the left anterior descending artery (LAD) (61.2%), followed by the right coronary artery (RCA; 30.6%), whereas plaque rupture was equally distributed in both the LAD and the RCA (47.0% and 43.3%, respectively). The majority of the culprit lesions were located in proximal and mid coronary segments with no significant difference in spatial distribution of erosion vs. rupture in three major epicardial arteries (*Figure 3A*). In the LAD, most erosions (89.1%) and ruptures (89.1%) tended to cluster within the first 40 mm from the coronary ostium, while only half of the erosions (51.6%) and ruptures (52.5%) were located within the first 40 mm and were more evenly distributed throughout the entire length of the RCA (*Figure 3B*). Multi-vessel disease was observed in 44.8% of STEMI patients, with a significant lower prevalence in patients with plaque erosion (29.7% vs. 50.4%, $P < 0.001$). Lesions with plaque erosion presented less frequently with initial thrombolysis in myocardial infarction (TIMI) flow grade ≤1 ($P = 0.001$) and required less frequent use of manual thrombectomy ($P = 0.006$). Quantitative coronary angiography data showed erosions were in larger vessels ($P < 0.001$) with a smaller post-thrombectomy diameter stenosis ($P < 0.001$) than ruptures.

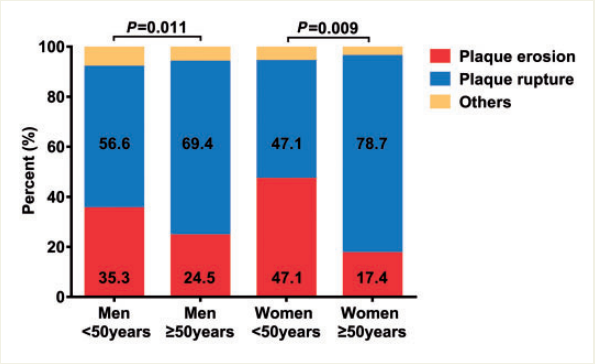


Figure 2 Prevalence of plaque erosion stratified by age and gender. Plaque erosion was more frequent in women <50 years when compared with those ≥50 years of age. A similar, but less striking difference was also observed in men.

Optical coherence tomography findings

The OCT findings are listed in *Table 3*. When compared with plaque rupture, plaque erosion had a lower prevalence of lipid-rich plaque and thin-cap fibroatheroma (TCFA); furthermore, among lipid-rich plaque, plaque erosion had less lipid content than plaque rupture. Other underlying plaque characteristics, including macrophages accumulation, microchannel, and calcification, were less frequently observed in erosion vs. rupture. MLA was significantly larger in plaque erosion than plaque rupture ($P = 0.001$). In 209 patients with plaque erosion, 181 (86.6%) of MLA were located at the site with maximal thrombus burden; 20 (9.6%) and 8 (3.8%) of MLA were located

Table 2 Angiographical findings

Variables	Overall ($n = 773$)	Plaque erosion ($n = 209$)	Plaque rupture ($n = 564$)	*P*-value
Infarct-related artery				0.002
LAD	393 (50.8)	128 (61.2)	265 (47.0)	
RCA	308 (39.8)	64 (30.6)	244 (43.3)	
LCX	72 (9.3)	17 (8.1)	55 (9.8)	
Culprit lesion site				0.475
Proximal segment	267 (34.5)	79 (37.8)	188 (33.3)	
Mid segment	357 (46.2)	90 (43.1)	267 (47.3)	
Distal segment	149 (19.3)	40 (19.1)	109 (19.3)	
Distance to the ostium (mm)	32.8 ± 21.3	31.3 ± 22.1	33.4 ± 21.1	0.234
Multi-vessel disease	346 (44.8)	62 (29.7)	284 (50.4)	<0.001
Initial TIMI flow ≤1	585 (75.7)	141 (67.5)	444 (78.7)	0.001
Manual thrombectomy	687 (88.9)	175 (83.7)	512 (90.8)	0.006
QCA data				
RVD (mm)	2.90 ± 0.55	3.02 ± 0.53	2.85 ± 0.55	<0.001
MLD (mm)	0.94 ± 0.43	1.09 ± 0.47	0.88 ± 0.40	<0.001
Diameter stenosis (%)	67.4 ± 13.8	64.4 ± 13.3	68.6 ± 13.8	<0.001
Lesion length (mm)	16.2 ± 7.3	16.4 ± 7.0	16.1 ± 7.4	0.620

Values are presented as *n* (%) or mean ± SD.
LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimal lumen diameter; QCA, quantitative coronary angiography; RCA, right coronary artery; RVD, reference vessel diameter; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.

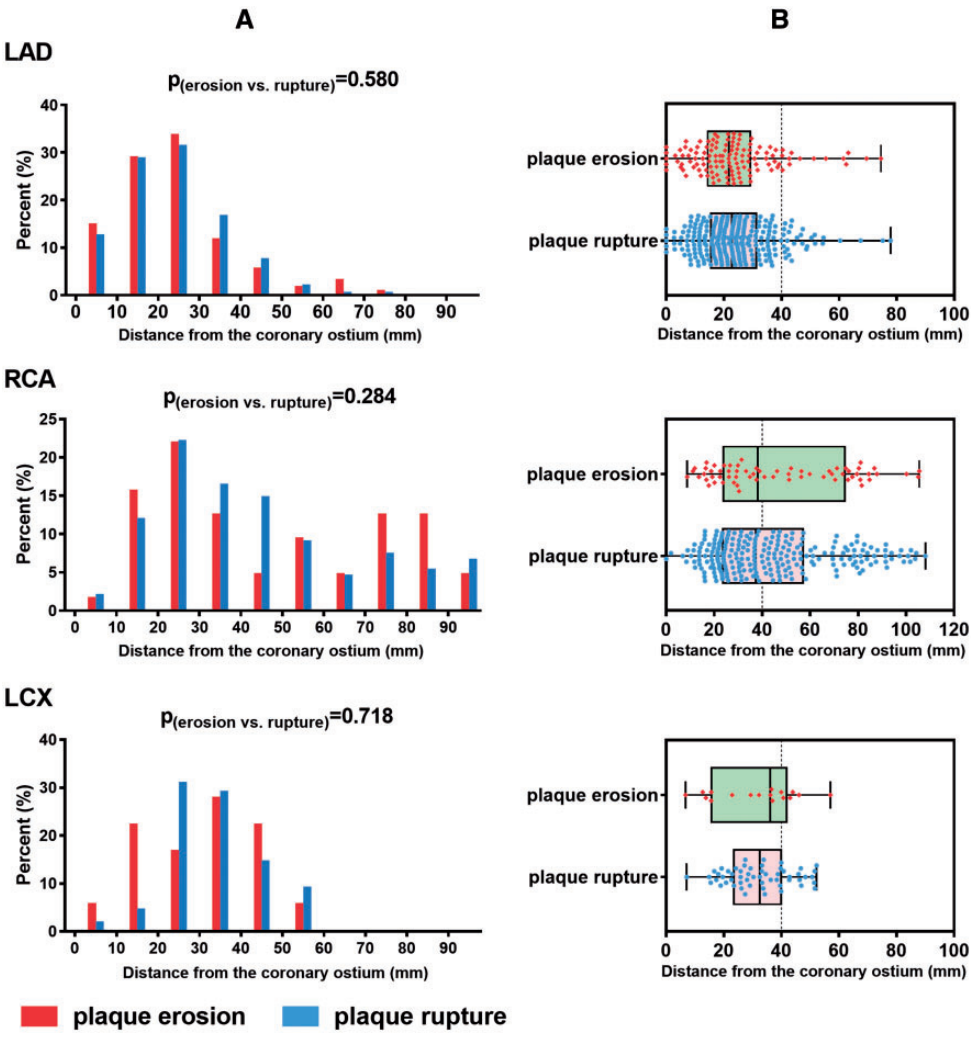


Figure 3 The spatial distribution of plaque erosion and plaque rupture in the coronary arteries. Bar graph (*A*): The spatial distribution of plaque erosion in three major epicardial arteries was similar to plaque rupture. Boxplots graph (*B*): In the LAD, most erosions (114/128, 89.1%) and ruptures (236/265, 89.1%) clustered within the first 40 mm from the coronary ostium. In the RCA, only half of erosions (33/64, 51.6%) and ruptures (128/244, 52.5%) were located within the first 40 mm and were more evenly distributed throughout the entire length of the coronary artery. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

proximal and distal, but adjacent to the maximal thrombus burden, respectively.

Plaque erosion was more frequently located near a bifurcation when compared with plaque rupture (59.3% vs. 34.6%, $P < 0.001$), particularly in the LAD (70.3% vs. 46.8%, $P < 0.001$). Notably, unlike ruptures, erosions tended to cluster immediately proximal or distal to a bifurcation (*Figure 4A*). Among them, 66.7% of erosions and 47.1% of ruptures were located within 3 mm near a bifurcation (*Figure 4B*). The distance to the nearby bifurcation was significantly shorter in plaque erosion than plaque rupture [2.3 mm (1.2–3.3 mm) vs. 3.1 mm (1.7–3.8 mm), $P = 0.003$].

Predictors of plaque erosion

In the overall cohort of 773 STEMI patients, the following variables with a *P*-value <0.1 in the univariate analysis (Supplementary material online, *Table S3*) were tested: age <50 years, men, current smoker, diabetes mellitus, hypertension, dyslipidaemia, CKD, TC, triglyceride, LDL-C, TC/HDL-C ratio, LAD, multi-vessel disease, initial TIMI flow ≤1, manual thrombectomy, reference vessel diameter (RVD), diameter stenosis, MLA, and nearby bifurcation. In the multivariable analysis, age <50 years, current smoker, absence of other coronary risk factors (hypertension, dyslipidaemia and CKD), lack of multi-vessel disease, smaller diameter stenosis, larger RVD, and nearby bifurcation were significantly associated with plaque erosion (*Figure 5*).

Variables with a *P*-value <0.1 in the univariate analysis in men (Supplementary material online, *Table S4*) and women (Supplementary material online, *Table S5*) separately were also tested in the multivariable model. The predictors of plaque erosion in men and women are shown in *Figure 5*. In both men and women, age

Table 3 Optical coherence tomography analysis

Variables	Overall ($n = 773$)	Plaque erosion ($n = 209$)	Plaque rupture ($n = 564$)	*P*-value
Plaque characteristics				
Lipid-rich plaque	649 (84.0)	98 (46.9)	551 (97.7)	<0.001
FCT (μm)	52.3 ± 26.2	89.0 ± 36.0	45.4 ± 16.6	<0.001
Mean lipid arc (°)	237.1 ± 47.2	219.7 ± 48.3	240.2 ± 46.4	<0.001
Lipid core length (mm)	12.3 ± 5.9	9.8 ± 5.1	12.7 ± 5.9	<0.001
TCFA	540 (69.9)	30 (14.4)	510 (90.4)	<0.001
Macrophages	618 (79.9)	107 (51.2)	511 (90.6)	<0.001
Microchannel	306 (39.6)	68 (32.5)	238 (42.2)	0.015
Calcification	331 (42.8)	54 (25.8)	277 (49.1)	<0.001
MLA (mm^2)	1.7 (1.3–2.3)	1.8 (1.4–2.8)	1.6 (1.3–2.2)	0.001
Nearby bifurcation	319 (41.3)	124 (59.3)	195 (34.6)	<0.001
LAD	214/393 (54.5)	90/128 (70.3)	124/265 (46.8)	<0.001
RCA	71/308 (23.1)	23/64 (35.9)	48/244 (19.7)	0.006
LCX	34/72 (47.2)	11/17 (64.7)	23/55 (41.8)	0.099

Values are presented as *n* (%), mean ± SD, or median (25th–75th percentile).
FCT, fibrous-cap thickness; LAD, left anterior descending artery; LCX, left circumflex artery; MLA, minimal lumen area; RCA, right coronary artery; SD, standard deviation; TCFA, thin-cap fibroatheroma.

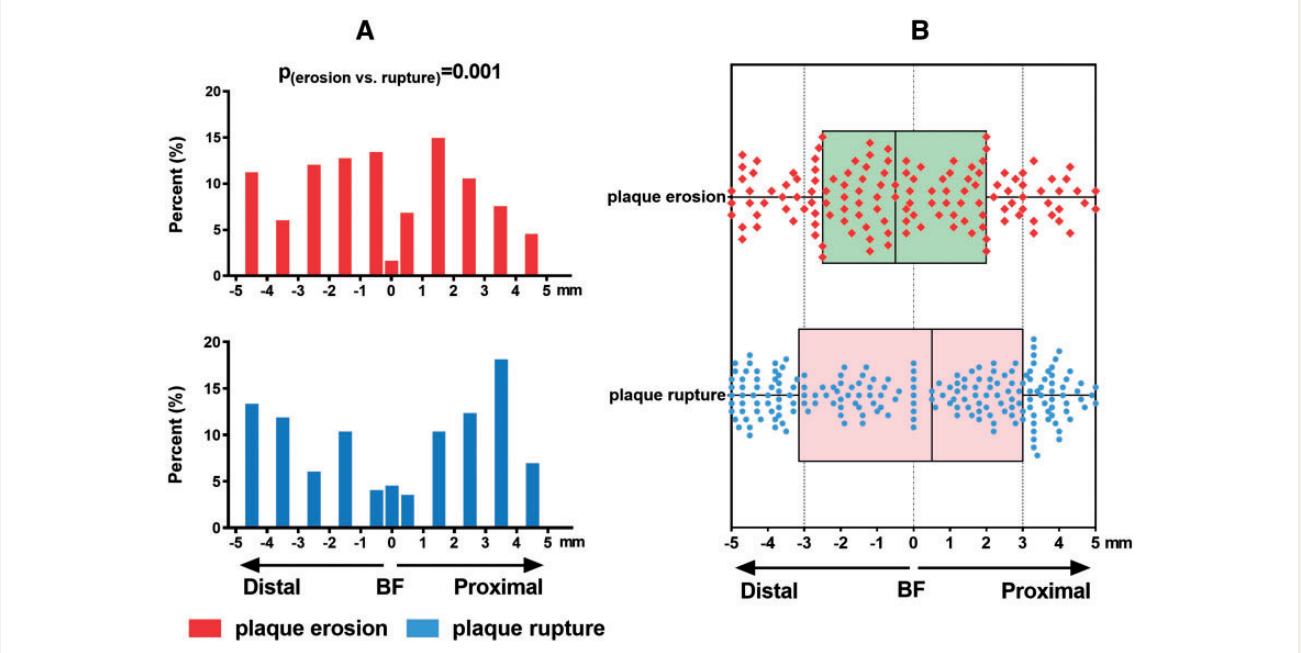


Figure 4 The distribution of plaque erosion and plaque rupture near a bifurcation. Bar graph (*A*): Different from ruptures, erosions tended to cluster immediately proximal or distal to a bifurcation. Boxplots graph (*B*): Among them, 66.7% of erosions and 47.1% of ruptures were located within 3 mm near a bifurcation. BF, bifurcation.

<50 years, nearby bifurcation, and absence of dyslipidaemia were predictive of plaque erosion. Current smoking was a risk factor of plaque erosion in men but not in women. Lesions with plaque erosion were less severe in men (absence of initial TIMI flow grade ≤1, smaller diameter stenosis, and larger MLA) but not in women. In women, absence of multi-vessel disease was significantly associated with plaque erosion; this was not seen in men.

Harrell's *c*-index corrected for 'optimism' via bootstrapping showed the discrimination of plaque erosion in the overall cohort, men, and women were 0.751, 0.750, and 0.723, respectively.

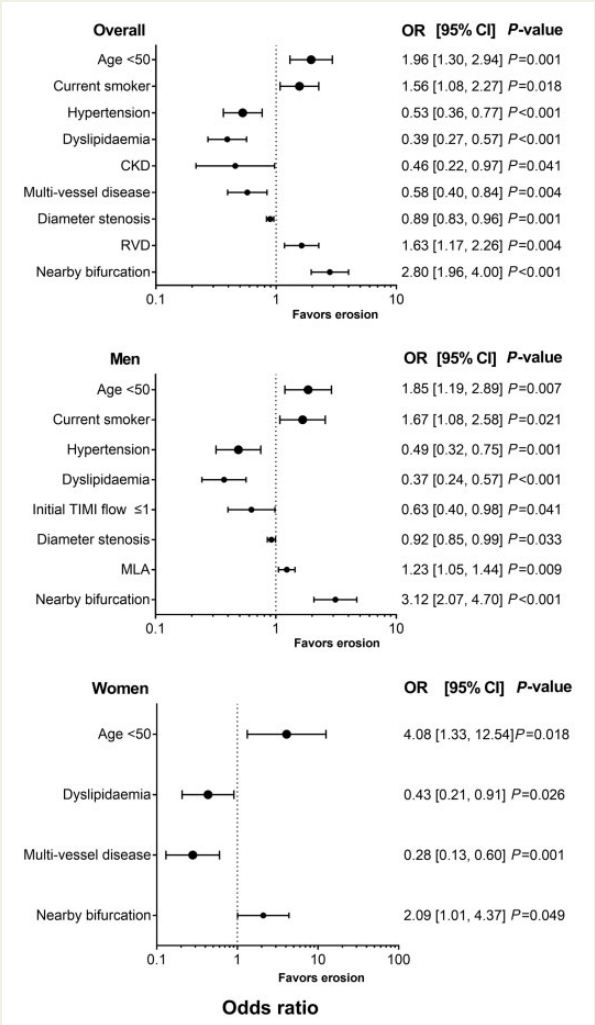


Figure 5 Predictors of plaque erosion. OR for diameter stenosis was calculated for each 5.0% increase, OR for RVD was calculated for each 1.0 mm increase, and OR for MLA was calculated for each 1.0 mm^2 increase. CI, confidence interval; CKD, chronic kidney disease; MLA, minimal lumen area; OR, odds ratio; RVD, reference vessel diameter; TIMI, thrombolysis in myocardial infarction.

Discussion

The present study extended previous pathological observations and provided new clinical understanding of plaque erosion in a large prospective series of STEMI patients. The main findings were as follows. (i) Plaque erosion tended to occur in younger patients, especially in pre-menopausal women. Age <50 years was a predictor of plaque erosion. (ii) Current smoking was the predominant coronary risk factor of plaque erosion rather than dyslipidaemia, hypertension, CKD, or diabetes mellitus. (iii) Plaque erosion was most frequently located in the LAD with a limited, focal distribution similar to plaque rupture, as well as proximity to a bifurcation. Nearby bifurcation was the strongest anatomical predictor of plaque erosion. (iv) Similarities and differences in predictors of plaque erosion were found between men and women.

Age, gender, and prevalence of plaque erosion

The prevalence of plaque erosion depended on age and gender. In a registry of 442 sudden coronary death (SCD) victims, women <50 years of age had a higher prevalence of plaque erosion when compared with women ≥50 years of age (84% vs. 32%); this was also demonstrated in men, but to a lesser degree (29% vs. 18%).[12] In previous OCT studies, patients with plaque erosion were younger than those with plaque rupture.[2,4] However, gender differences between the two substrates (i.e. erosion vs. rupture) were not confirmed *in vivo*, and the prevalence of plaque erosion in specific age groups of men and women remains largely unknown. The current study of patients presenting to a busy STEMI treatment facility demonstrated that plaque erosion occurred primarily in patients under the age of 50 years and represented approximately 50% of STEMI in pre-menopausal women. In women ≥50 years of age, approximately 80% of STEMI were caused by plaque rupture.

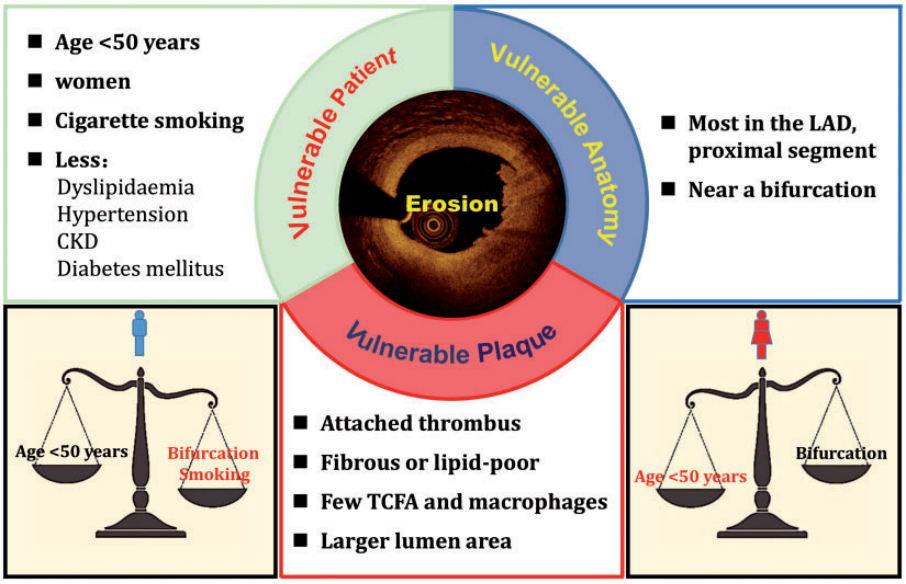
Coronary risk factors of plaque erosion vs. plaque rupture

Pathological data are few and inconsistent regarding coronary risk factors associated with erosion vs. rupture. Cigarette smoking seems to promote thrombosis rather than atherosclerosis in younger patients but may be a factor contributing to plaque rupture in more elderly patients. Burke *et al.*[13,14] reported a positive correlation between smoking and thrombosis in victims of SCD and more so in pre-menopausal women with plaque erosion when compared with plaque rupture. Kojima *et al.*[15] suggested that smoking was related with plaque rupture in elderly (average age ≈70 years). In an intravascular ultrasound study, Kang *et al.*[16] demonstrated that current smoking was associated with echolucent plaques and plaque rupture in patients >65 years but not in patients ≤65 years. In the present study, current smoking was the predominant coronary risk factor of plaque erosion in the overall cohort of STEMI patients with an average age of 57.7 years. Smoking cessation appears to be the major risk factor modification indicated for plaque erosion, particularly in younger patients.

Post-mortem studies revealed that subjects with plaque erosion had a lower TC level and a lower TC/HDL-C ratio than plaque rupture, similar to our results.[13,14] By multivariable analysis, absence of dyslipidaemia was strongly associated with plaque erosion. Therefore, plaque erosion may contribute importantly to the residual atherothrombotic risk in the current era of intensive lipid lowering. Patients with hypertension and CKD had more typical vulnerable plaques and ruptures, also consistent with our observations.[13,14,17] Burke *et al.*[13,14] found no association between diabetes mellitus and the type of thrombosis in SCD victims, while one OCT study observed that diabetes mellitus was associated with both TCFA and plaque erosion.[18] In the present study, diabetes mellitus was not a predictor of underlying substrates (i.e. erosion vs rupture). Regarding inflammatory biomarker, pathological study suggested that hs-CRP level was similar for patients with erosion vs. rupture,[19] again confirmed in the present study.

Plaque distribution, nearby bifurcation, and plaque erosion

Despite the fact that the entire arterial tree was exposed to systemic coronary risk factors, previous studies have shown that acute



Take home figure Plaque erosion is a predictable clinical entity, including vulnerable patient, vulnerable anatomy, and vulnerable plaque in patients with ST-segment elevation myocardial infarction. Plaque erosion tends to occur in younger patients, especially in pre-menopausal women. Age <50 years is a predictor of plaque erosion. Cigarette smoking is the predominant coronary risk factor of plaque erosion rather than dyslipidaemia, hypertension, CKD, or diabetes mellitus. Plaque erosion is most frequently located in the LAD within the proximal segment as well as proximity to a bifurcation. Nearby bifurcation is the strongest anatomical predictor of plaque erosion. Thrombus associated with plaque erosion generally overlies fibrous or lipid-poor plaques with few TCFA and macrophages but have larger lumen area. Nearby bifurcation and smoking are especially notable in men while age <50 years is most predictive in women. CKD, chronic kidney disease; LAD, left anterior descending artery; TCFA, thin-cap fibroatheroma.

coronary occlusions, TCFAs, and ruptures clustered predominantly in the proximal segment of the LAD but was more evenly distributed throughout the RCA.[20,21] However, to our knowledge, the spatial distribution of plaque erosion has not been systematically investigated. We extended previous studies by demonstrating that plaque erosion was most frequently located in the LAD with a limited, focal distribution similar to plaque rupture. In line with us, Kramer *et al.*[22] examined 111 SCD victims and reported that greater frequencies of erosions were found in the LAD (66%), with fewer lesions in the RCA (22%), whereas ruptures were more equally distributed in both the LAD and RCA (40% and 35%, respectively). Intriguingly, we found that approximately 60% of erosions clustered near a bifurcation, particularly in the LAD (70.3%). Nearby bifurcation emerged as the strongest anatomical predictor of plaque erosion. Although the current study did not allow dissecting underlying pathophysiological mechanisms, these observations suggested that local haemodynamic factors may play a critical role in plaque erosion without the help of systemic coronary risk factors (i.e. dyslipidaemia, hypertension, CKD, and diabetes mellitus). The side branch affects shear stress in the nearby (within 3 mm) associated main branch.[23] Recently, Franck *et al.*[24] found that disturbed blood flow may lead to chronic endothelial activation, propensity to slough, and localized neutrophils cooperate to drive endothelial denudation and arterial thrombosis in a murine model of superficial erosion. The absence of branches in the RCA may be the explanation for the differences between the RCA and the LAD.

Predictors in men vs. women

The present study demonstrated both similarities and differences between men and women in the predictors of plaque erosion. Age <50 years, nearby bifurcation, and absence of dyslipidaemia were predictive of plaque erosion, regardless of gender. The association between current smoking and plaque erosion was not observed in women but in men, which is contrary to pathological observations.[13,14] This discrepancy could be due to the age of onset of STEMI (62.7 years vs. 55.7 years) and a lower prevalence of current smoking (36.7% vs. 62.4%) in women when compared with men. It is noteworthy that subjects evaluated in post-mortem studies were relatively young with no significant difference in the average age of SCD between women and men (50 years vs. 48 years).[12–14] Culprit lesions with plaque erosion were less severe than plaque rupture in men. However, the role of menopause is unique for women. Oestrogen has been suggested to retard plaque development, stabilize existing plaques, and prevent plaque rupture in pan-coronary artery, but increase the risk of thrombosis.[12,13] Accordingly, age <50 years was the strongest predictor of plaque erosion in women, and absence of multi-vessel disease was significantly associated with plaque erosion.

Study limitations

There are several limitations that should be acknowledged. First, the data were acquired in predominantly young patients with a high prevalence of smoking, reflecting the current epidemiological

characteristics of Chinese STEMI patients. Therefore, the results may not be generalizable to other countries or to NSTE-ACS patients. Second, highly unstable patients or those with complex coronary anatomy were not included in this study. Third, the current OCT system cannot visualize individual endothelial cells. Therefore, the OCT definition of plaque erosion is in some ways an exclusive diagnosis. Fourth, thrombectomy may affect lesion morphology and cause plaque rupture iatrogenically. However, thrombectomy was not independently associated with the underlying plaque morphology (i.e. erosion vs. rupture) in the multivariable analysis. In the 86 patients without thrombectomy before OCT imaging, age <50 years, absence of dyslipidaemia, lack of multi-vessel disease, smaller diameter stenosis, and nearby bifurcation were still predictors of plaque erosion. Fifth, OCT has limited penetration, especially in the setting of lipid or a necrotic core, precluding assessment of vessel size, plaque burden, remodelling, and lesion eccentricity. Sixth, a large residual thrombus might obscure the lumen border and underlying plaque, making it difficult to assess the underlying plaque characteristics and distinguish plaque rupture from plaque erosion. We, therefore, excluded patients with massive residual thrombus from analysis. Finally, while not currently available, long-term follow-up of this large prospective series of STEMI patients is in progress.

Conclusions

Plaque erosion was a predictable clinical entity distinct from plaque rupture in one-quarter of STEMI patients. Specific role of risk factors in plaque erosion should be considered in men and women. These findings may herald a paradigm shift in targeting coronary risk factors modification, comprehensive atherothrombotic risk evaluation (i.e. age, gender, systemic coronary risk factors, local anatomical and hemodynamic factors, and plaque characteristics) and tailored management in patients with plaque erosion (*Take home figure*).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

National Natural Science Foundation of China (grant no. 81330033 to B.Y., grant no. 81200076 to H.J., and grant no. 81671794 to J.H.); National Key R&D Program of China (grant no. 2016YFC1301100 to B.Y.).

Conflict of interest: G.S.M. has received research grants from St. Jude Medical, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. All other authors have reported that they have no shareholding in or receipt of a grant or consultancy fee from a company whose product features in the submitted manuscript or which manufactures a competing product.

References

1. Farb A, Burke AP, Tang AL, Liang TY, Mannan P, Smialek J, Virmani R. Coronary plaque erosion without rupture into a lipid core. A frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996;**93**:1354–1363.
2. 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**:1748–1758.
3. 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**:1377–1384.
4. Higuma T, Soeda T, Abe N, Yamada M, Yokoyama H, Shibutani S, Vergallo R, Minami Y, Ong DS, Lee H, Okumura K, Jang IK. A combined optical coherence tomography and intravascular ultrasound study on plaque rupture, plaque erosion, and calcified nodule in patients with ST-segment elevation myocardial infarction: incidence, morphologic characteristics, and outcomes after percutaneous coronary intervention. *JACC Cardiovasc Interv* 2015;**8**:1166–1176.
5. Durand E, Scoazec A, Lafont A, Boddaert J, Al Hajzen A, Addad F, Mirshahi M, Desnos M, Tedgui A, Mallat Z. In vivo induction of endothelial apoptosis leads to vessel thrombosis and endothelial denudation: a clue to the understanding of the mechanisms of thrombotic plaque erosion. *Circulation* 2004;**109**:2503–2506.
6. Quillard T, Araujo HA, Franck G, Shvartz E, Sukhova G, Libby P. TLR2 and neutrophils potentiate endothelial stress, apoptosis and detachment: implications for superficial erosion. *Eur Heart J* 2015;**36**:1394–1404.
7. 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.
8. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
9. Crea F, Libby P. Acute coronary syndromes: the way forward from machanisms to precision treatment. *Circulation* 2017;**136**:1155–1166.
10. 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;doi: 10.1093/eurheartj/ehx786. Published online ahead of print 9 January 2018.
11. Hu S, Yonetsu T, Jia H, Karanasos A, Aguirre AD, Tian J, Abtahian F, Vergallo R, Soeda T, Lee H, McNulty I, Kato K, Yu B, Mizuno K, Toutouzas K, Stefanadis C, Jang IK. Residual thrombus pattern in patients with ST-segment elevation myocardial infarction caused by plaque erosion versus plaque rupture after successful fibrinolysis: an optical coherence tomography study. *J Am Coll Cardiol* 2014;**63**:1336–1338.
12. Yahagi K, Davis HR, Arbustini E, Virmani R. Sex differences in coronary artery disease: pathological observations. *Atherosclerosis* 2015;**239**:260–267.
13. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* 1998;**97**:2110–2116.
14. Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R. Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. *N Engl J Med* 1997;**336**:1276–1282.
15. Kojima S, Nonogi H, Miyao Y, Miyazaki S, Goto Y, Itoh A, Daikoku S, Matsumoto T, Morii I, Yutani C. Is preinfarction angina related to the presence or absence of coronary plaque rupture? *Heart* 2000;**83**:64–68.
16. Kang SJ, Mintz GS, Weisz G, Mehran R, Rabbani LE, Verheye S, Serruys PW, Xu K, Stone GW, Maehara A. Age-related effects of smoking on coronary artery disease assessed by gray scale and virtual histology intravascular ultrasound. *Am J Cardiol* 2015;**115**:1056–1062.
17. Dai J, Xing L, Hou J, Jia H, Hu S, Tian J, Lin L, Li L, Zhu Y, Zheng G, Zhang S, Yu B, Jang IK. Chronic kidney disease predicts coronary plaque vulnerability: an optical coherence tomography study. *Coron Artery Dis* 2017;**28**:135–144.
18. De Rosa R, Vasa-Nicotera M, Leistner DM, Reis SM, Thome CE, Boeckel JN, Fichtlscherer S, Zeiher AM. Coronary atherosclerotic plaque characteristics and cardiovascular risk factors: insights from an optical coherence tomography study. *Circ J* 2017;**81**:1165–1173.
19. Burke AP, Tracy RP, Kolodgie F, Malcom GT, Zieske A, Kutys R, Pestaner J, Smialek J, Virmani R. Elevated C-reactive protein values and atherosclerosis in sudden coronary death: association with different pathologies. *Circulation* 2002;**105**:2019–2023.
20. Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 2004;**110**:278–284.

21. Cheruvu PK, Finn AV, Gardner C, Caplan J, Goldstein J, Stone GW, Virmani R, Muller JE. Frequency and distribution of thin-cap fibroatheroma and ruptured plaques in human coronary arteries: a pathologic study. *J Am Coll Cardiol* 2007;**50**: 940–949.
22. Kramer MC, Rittersma SZ, de Winter RJ, Ladich ER, Fowler DR, Liang YH, Kutys R, Carter-Monroe N, Kolodgie FD, van der Wal AC, Virmani R. Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. *J Am Coll Cardiol* 2010;**55**:122–132.
23. Gijsen FJ, Wentzel JJ, Thury A, Lamers B, Schuurbiers JC, Serruys PW, van der Steen AF. A new imaging technique to study 3-D plaque and shear stress distribution in human coronary artery bifurcations in vivo. *J Biomech* 2007;**40**:2349–2357.
24. Franck G, Mawson T, Sausen G, Salinas M, Masson GS, Cole A, Beltrami-Moreira M, Chatzizisis Y, Quillard T, Tesmenitsky Y, Shvartz E, Sukhova GK, Swirski FK, Nahrendorf M, Aikawa E, Croce KJ, Libby P. Flow perturbation mediates neutrophil recruitment and potentiates endothelial injury via TLR2 in mice: implications for superficial erosion. *Circ Res* 2017;**121**:31–42.