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Impact of Culprit Plaque and Atherothrombotic Components on Incomplete Stent Apposition in Patients With ST-Elevation Myocardial Infarction Treated With Everolimus-Eluting Stents

– An OCTAVIA Substudy –

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Background: The role of culprit plaque and related atherothrombotic components on incomplete stent apposition (ISA) occurrence after primary percutaneous coronary intervention (p-PCI) is unknown.

Methods and Results: ST-segment elevation myocardial infarction (STEMI) patients undergoing p-PCI with an everolimus-eluting stent were prospectively investigated with optical coherence tomography (OCT) of the infarct-related artery before, after stenting and at 9 months. OCT data, aspirated thrombus and serum inflammatory biomarkers were analyzed. 114 patients with 114 lesions were evaluated. Acute ISA occurred in 82 lesions (71.9%), preferentially in larger vessels with a median area of 0.2 mm^2. The presence of thrombus before stent implantation (odds ratio (OR) 5.5, 95% confidence interval (CI) [1.1–26.9], P=0.04) and the lipid content in the target segment (OR 1.3, 95% CI [1.0–1.5], P=0.04) independently predicted acute ISA. At 9-month follow-up, ISA persisted in 46 lesions (56.1%). The volume of acute ISA significantly predicted persistent ISA (OR 1.3, 95% CI [1.1–1.5], P=0.01). Late-acquired ISA occurred in 39 lesions (34.2%) with a median area of 0.3 mm^2. Red/mixed thrombus before stent implantation (OR 3.7, 95% CI [1.0–13.3], P=0.05) and length of the underlying ruptured plaque (OR 1.7, 95% CI [1.1–2.8] P=0.02) were independently associated with late-acquired ISA.

Conclusions: In STEMI patients, culprit plaque and atherothrombotic components of the infarct-related artery significantly contribute to the onset of acute and late ISA. ISA persistence at follow-up depends on the initial volume of acute ISA. (*Circ J* 2016; **80:** 895–905)

Key Words: Acute myocardial infarction; Drug-eluting stent; Everolimus-eluting stent; Incomplete stent apposition; Optical coherence tomography

Stent implantation in the setting of primary percutaneous coronary intervention (p-PCI) has been linked with an increased risk of early and late incomplete stent apposition (ISA).[1,2] Importantly, despite the lack of a compelling evidence, multiple studies have highlighted the putative association between ISA and stent thrombosis,[2–4] outlining the importance of investigations aimed at understanding and possibly preventing this phenomenon. Several mechanisms have already been advocated to explain why ISA occurs more frequently in patients with ST-segment elevation myocardial

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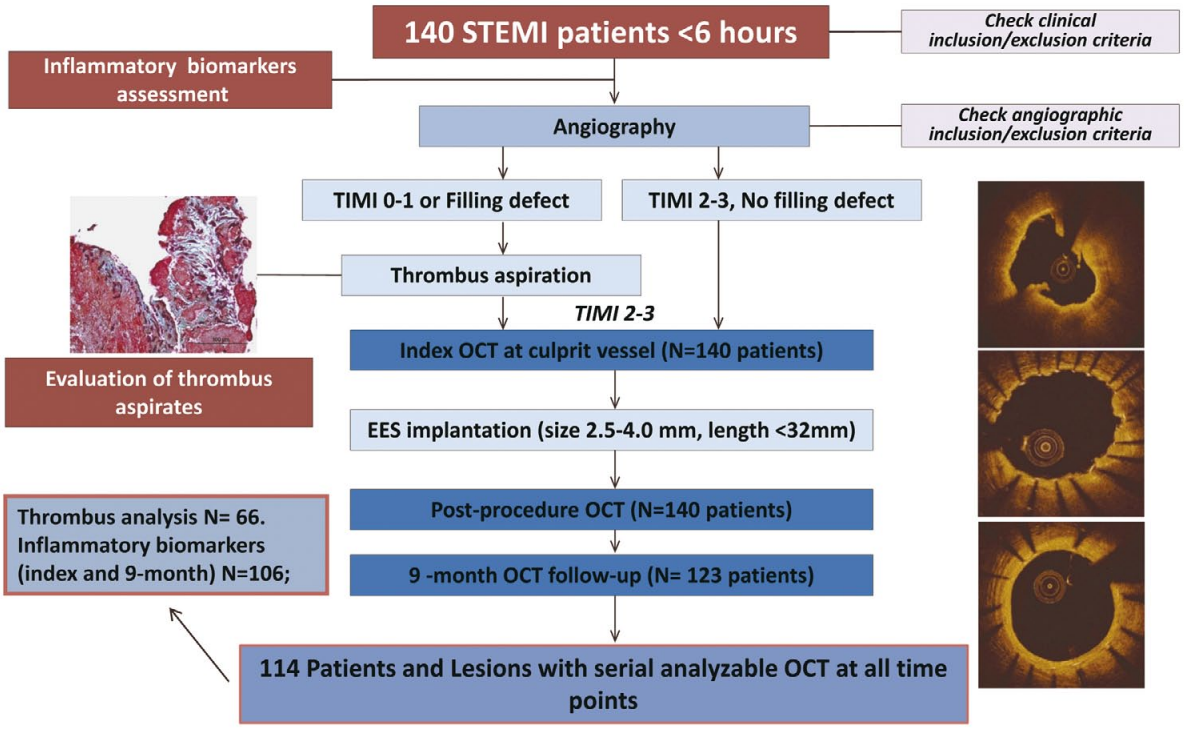

Figure 1. Study flow chart summarizes the procedures and reports the number of patients enrolled in the main OCTAVIA trial and in the present analysis. EES, everolimus-eluting stent; OCT, optical coherence tomography; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction.

infarction (STEMI) undergoing p-PCI.[1,2,5,6] First, thrombus deposition and systemic adrenergic vasoconstriction might prevent accurate assessment of coronary dimensions, resulting in stent under-sizing. Second, positive vessel remodeling and/or dissolution of abluminal thrombus initially trapped by the stent struts may result in late ISA. Third, drug-eluting stents (DES) themselves have been associated with an enhanced risk of late-ISA owing to delayed vessel healing.[3–6] Against this background, however, it is remarkable that the effect of culprit plaque and atherothrombotic components responsible for STEMI on early and late ISA has never been prospectively investigated. Therefore, the aim of the present study was to investigate the implication of plaque characteristics and related atherothrombotic components on the incidence of acute, persistent and late-acquired ISA following p-PCI with current-generation everolimus-eluting-stents (EES).

Methods

Study Population

The present study represents a prespecified analysis of the OCTAVIA trial (clinicaltrials.gov identifier NCT01377207) focusing on mechanisms underlying ISA. The protocol design, the full methodology and results of the OCTAVIA study have been reported elsewhere.[7] Briefly, OCTAVIA was a prospective, multicenter, investigator-driven study assessing atherothrombotic mechanisms and vascular response to stenting in age-matched women and men presenting with STEMI and undergoing p-PCI with EES (Xience Prime, Abbott Vascular, Santa Clara, CA, USA). All decisions regarding stent position, stent size and length, requirement for pre- and post-dilatation, balloon size and the assessment of optimal stent expansion were based on angiography alone, and left to the discretion of the operator. By protocol, patients enrolled in OCTAVIA underwent optical coherence tomography (OCT) of the IRA (1) before, (2) immediately after EES implantation and (3) at 9-month elective follow-up. Only patients having OCT pullbacks of the IRA fully analyzable and comparable at all prespecified time points were eligible for this analysis (Figure 1). Histopathology and immunohistochemistry of thrombus aspirates retrieved during p-PCI and serum inflammatory biomarkers obtained at clinical presentation and 9-month follow-up were additionally evaluated, as described later. The ethical committee at each clinical site approved the study protocol and written informed consent was given by all patients.

Angiographic Analysis

Quantitative coronary angiography was performed after administration of 200 μg intracoronary nitroglycerin at pre- and post-procedure and at follow-up. Digital coronary angiograms were analyzed offline at the angiographic core laboratory (Cardiovascular Imaging Core Laboratory; University Hospitals Case Medical Center, Cleveland, OH, USA), using a validated automated edge detection system (CAAS II, PIE Medical, Maastricht, The Netherlands). Measurements were made from at least 2 comparable orthogonal projections of the IRA. Reference vessel diameter (RVD), minimum luminal diameter,

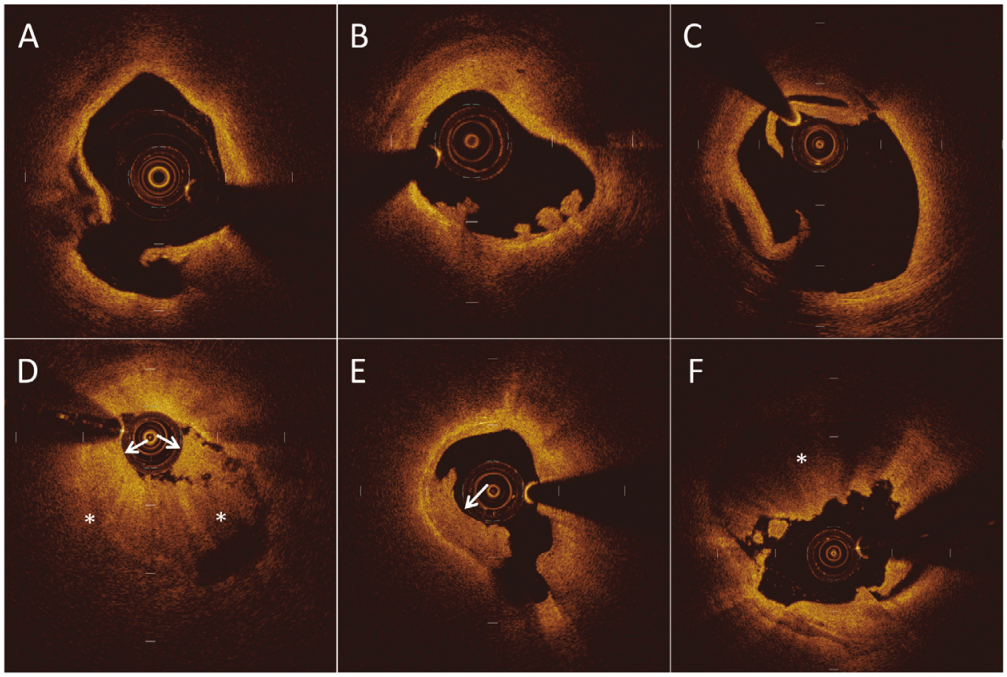

Figure 2. OCT findings of culprit plaque and thrombus in the infarct-related artery. Culprit plaque phenotypes were classified as ruptured (**A**); non-rupture/eroded plaque (**B**); spontaneous dissection (**C**); unclassifiable etiology (**D**). Intracoronary thrombi, defined as an intraluminal mass with irregular contour floating within the lumen or attached to the intimal surface, were characterized as white (arrow) (**E**) with homogeneous signal-rich, low backscattering attenuation; red (*) (**F**) characterized by high backscattering and high light attenuation (shadowing effect); or mixed (**D**), a combination of both white (arrows) and red (*) with heterogeneous light signal properties. OCT, optical coherence tomography.

and percent diameter stenosis were assessed as per standard definitions.[8]

OCT Analysis

Serial OCT images of the IRA were acquired with a frequency domain-OCT system (C7-XRTM FD-OCT Intravascular Imaging System, St. Jude Medical, St. Paul, MN, USA) and analyzed by an independent core laboratory (Cardiovascular Imaging Core Laboratory, University Hospitals Case Medical Center). Two independent readers performed all the analyses. All cross-sectional images were screened for quality and excluded from analysis if any portion was out of the screen, if a side branch occupied >45° of the cross-section, or if the image had poor quality caused by suboptimal blood clearance, excessive residual thrombus or artifacts. In case of multiple pullbacks, integrated information was obtained by using fiducial points (ie, stent edges, side branches). Dedicated software (OCT system software B.0.1, LightLab) was used for quantification. Qualitative assessment was performed every 0.2 mm, whereas quantitative and morphometric analyses were performed every 0.6 mm along the entire target segment.[7] To determine the effect of plaque characteristics and atherothrombotic components on ISA, multiple OCT pullbacks were integrated. Each cross-section of the stented segment was matched with the corresponding cross-section obtained at baseline and at follow-up, as accurately as possible, based on distances from fiduciary axial landmarks (ie, side branches, calcification, stent edges) (**Figure S1**). Plaque morphology, atherothrombotic components and thrombus characteristics were classified according to accepted OCT definitions and criteria.[9,10] An "unclassified etiology" was assigned when the core laboratory was unable to adjudicate the occurrence of plaque rupture or erosion because of excessive residual thrombus that obscured the underlying structures. Rupture length was defined as the length with evidence of an intimal disruption in the ruptured plaque. Illustrative OCT examples of different culprit plaque phenotypes and the OCT thrombus classification used for the purposes of this study are shown in **Figure 2**. For the morphometric analysis, standard definitions of cross-sectional area and volume measurements were applied as previously reported.[9] The minimum stent cross-section area (CSA) divided by the average of proximal and distal reference lumen CSA ratio was calculated as a metric of stent expansion. Volumes (stent, lumen, ISA and neointima) were calculated according to the Simpson's rule. At follow-up, stent struts were termed covered if tissue was detected above the struts, and uncovered if no evidence of tissue was observed.[9]

ISA Definitions and Characterization

ISA was defined as a lack of contact between the stent struts and the underlying vessel wall, with evidence of blood speckle behind the struts in a segment not associated with any side branch.[2,5] A distance higher than the sum of the strut thickness plus the abluminal polymer thickness based on the specifications from the manufacturer, and a compensation factor of 18 μm to correct for strut blooming were considered for ISA

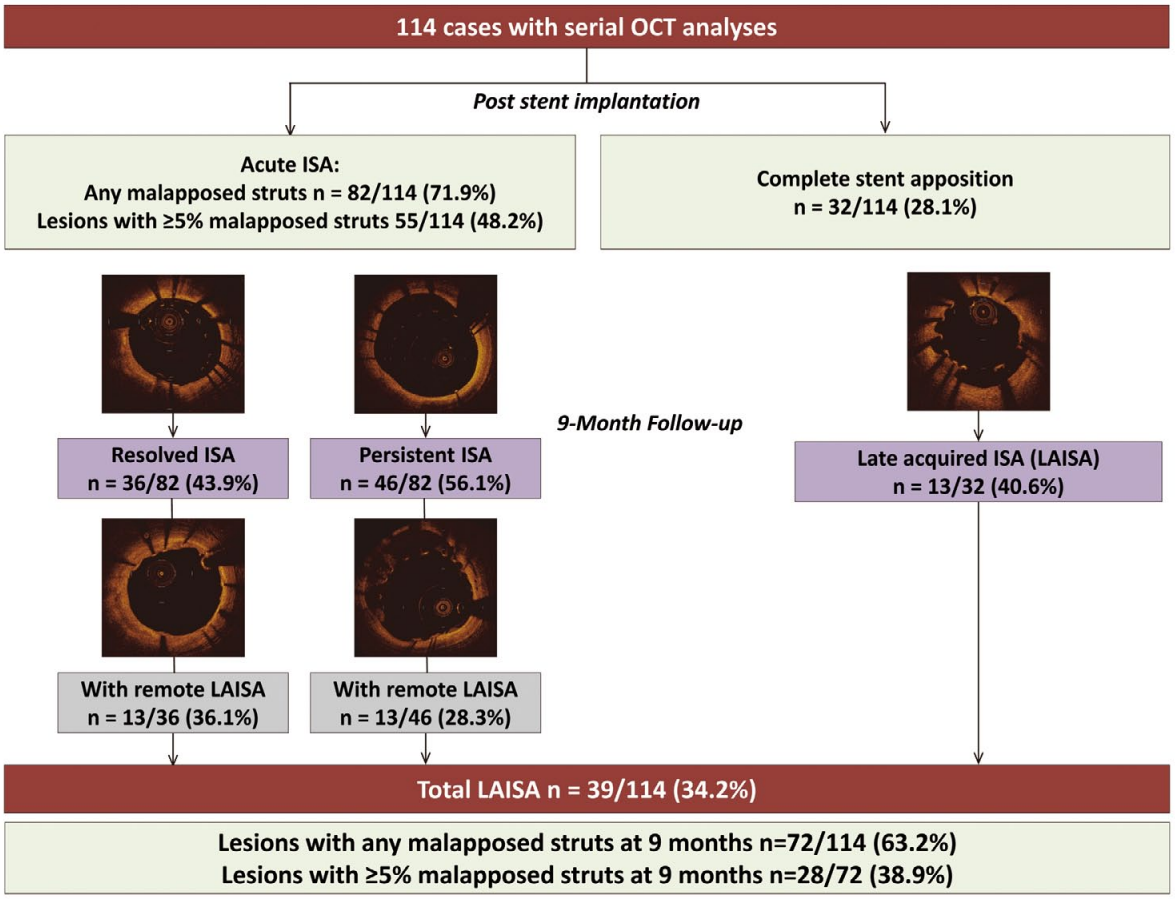

Figure 3. ISA in the study population. The incidence of acute, persistent and late-acquired ISA as detected by OCT immediately after EES implantation and at 9-month follow-up is reported. EES, everolimus-eluting stent; ISA, incomplete stent apposition; LAISA, late-acquired ISA.

adjudication.[7] ISA was core-laboratory adjudicated in the presence of ≥1 incompletely apposed strut. A prespecified subgroup of interest was composed of stents with ≥5% of malapposed struts, based on prior evidence.[11] ISA was labeled as acute (ie, detected immediately after stent deployment), persistent (ie, diagnosed post-procedure and persisting at follow-up), resolved (ie, diagnosed post-procedure and resolved at follow-up) or late acquired (ie, not present post-procedure but identified at 9-month follow-up). ISA quantification was accomplished by measuring the ISA distance, area, and volume. ISA distance was measured from the center of the strut blooming to the adjacent lumen border and expressed as the maximum distance. The ISA area was defined as the space between the lumen contour and the stent contour at the location of malapposed struts. To get the mean ISA area per patient, all the ISA areas were summed and divided by the total number of analyzed frames.[12] Once a complete set of ISA cross-sectional area measurements was obtained, ISA volume was calculated by Simpson's rule. The measurement methods were applied only in the ISA with longest length when multiple independent ISA were observed in 1 stent. The maximum length of ISA was defined as the number of consecutive cross-sections with malapposed struts. The locations of ISA were categorized as stent edge (<5 mm within the proximal or distal edge of the stent) or stent body.

Histopathology and Immunohistochemistry of Thrombus Aspirates

Thrombus aspirates, if any, were collected and sent for processing after fixation to an independent histopathology core laboratory (CV Path Institute Gaithersburg, MD, USA).[7] All sections were examined by light microscopy for the presence of platelets, fibrin, red blood cells, and plaque constituents. Additionally, immunohistochemical staining, including the granulocyte marker myeloperoxidase (MPO), CD68 (macrophages), and the eosinophil marker interleukin-5, was performed to further characterize the prevalence of specific inflammatory cell types.

Serum Biomarkers

Blood samples were drawn at baseline and at 9-month follow-up, and analyzed by an independent core laboratory (Institute of Cardiology, Catholic University of the Sacred Heart, Rome, Italy). Serum analyses included high-sensitivity C-reactive protein (hs-CRP), MPO, eosinophil cationic protein (ECP), and thromboxane B_2.[7]

Table 1. Angiographic and Procedural Characteristics of Lesions With and Without Acute, Persistent or Late-Acquired ISA

Variable	Acute ISA (+) (n=82)	Acute ISA (−) (n=32)	P value	Persistent ISA (n=46)	Resolved ISA (n=36)	P value	LAISA (+) (n=39)	LAISA (−) (n=75)	P value
Target vessel			0.07			0.87			0.23
LAD	32 (39.0)	12 (37.5)		17 (37.0)	15 (41.7)		11 (28.2)	33 (44.0)	
Left circumflex	4 (4.9)	6 (18.8)		2 (4.3)	2 (5.5)		3 (7.7)	7 (9.3)	
Right coronary	46 (56.1)	14 (43.7)		27 (58.7)	19 (52.8)		25 (64.1)	35 (46.7)	
Baseline TIMI flow grade			0.91			0.30			0.27
0/1	46 (56.1)	19 (59.4)		23 (50.0)	23 (63.9)		26 (66.7)	39 (52.0)	
2	28 (34.1)	9 (28.1)		19 (41.3)	9 (25.0)		9 (23.1)	28 (37.3)	
3	8 (9.8)	4 (12.5)		4 (8.7)	4 (11.1)		4 (10.2)	8 (10.7)	
Reference vessel diameter, mm	2.7 [2.4–3.1]	2.5 [2.1–2.9]	0.02	2.7 [2.4–3.3]	2.8 [2.4–3.0]	0.45	2.8 [2.4–3.3]	2.6 [2.3–2.9]	0.05
% Diameter stenosis	88.4±14.6	86.9±18.3	0.20	86.5±18.5	90.9±13.1	0.16	88.5±16.8	87.8±15.1	0.58
Calcification	8 (9.8)	1 (3.1)	0.44	5 (10.9)	3 (8.3)	0.73	2 (5.1)	7 (9.3)	0.35
Thrombus aspiration	71 (86.6)	26 (81.3)	0.26	39 (84.8)	32 (88.9)	0.42	33 (84.6)	64 (85.3)	0.56
Direct stenting	71 (86.6)	26 (81.3)	0.56	41 (89.1)	30 (83.3)	0.52	27 (69.2)	41 (54.7)	0.10
Stents implanted per lesion, n	1.3±0.7	1.3±0.3	0.68	1.3±0.7	1.4±0.6	0.29	1.3±0.6	1.3±0.6	0.98
Stent diameter, mm	3.0 [3.0–4.0]	3.0 [2.5–3.0]	0.18	3.0 [3.0–4.0]	3.0 [2.5–3.0]	0.58	3.0 [3.0–4.0]	3.0 [2–4]	0.18
Total stent length, mm	22.8 [17.7–31.1]	21.3 [15.2–28]	0.07	22.6 [17.7–28.4]	27.8 [17.9–32.9]	0.27	22.9 [17.7–32.1]	22.2 [17.5–29]	0.37
Minimum lumen diameter, mm	2.5 [2.2–3]	2.3 [2.2–2.6]	0.06	2.5 [2.1–3.0]	2.5 [2.2–2.8]	0.39	2.7 [2.3–3.0]	2.4 [2.1–2.8]	0.01
Post-dilation	50 (61)	16 (50.0)	0.26	31 (67.4)	19 (52.8)	0.13	17 (43.6)	49 (65.3)	0.02
Maximum pressure, atm	20.0 [16.5–23.5]	20.0 [14.5–20.0]	0.17	20.0 [16.5–23.5]	20.0 [14.5–20.0]	0.27	18.0 [15.0–20.0]	20.0 [15.0–20.0]	0.18
Acute gain, mm	2.3 [1.8–2.7]	2.2 [1.7–2.6]	0.34	2.2 [1.9–2.8]	2.3 [1.9–2.7]	0.87	2.4 [1.9–3.0]	2.2 [1.8–2.5]	0.05
Final TIMI flow grade			0.12			0.22			0.66
0/1	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
2	6 (7.3)	0 (0.0)		5 (10.9)	1 (2.8)		1 (2.6)	5 (6.7)	
3	76 (92.7)	32 (100.0)		41 (89.1)	35 (97.2)		38 (97.4)	70 (93.3)	

Data are presented as n/N (%), mean±standard deviation, or median [1st–3rd quartile]. ISA, incomplete stent apposition; LAD, left anterior descending artery; LAISA, late-acquired ISA; TIMI, Thrombolysis In Myocardial Infarction.

Clinical Endpoints

Major adverse cardiac or cerebrovascular events, including cardiac death, recurrent MI, stroke, or ischemia-driven target lesion revascularization, were evaluated up to 24 months. ST was assessed and defined according to the Academic Research Consortium definitions.[13]

Statistical Analysis

Patient, lesion and procedural characteristics and event rates were analyzed using descriptive statistics with SPSS 20.0 (IBM, Armonk, NY, USA). Categorical data are reported as simple proportions. Continuous data are reported as mean±standard deviation, or median [1st–3rd quartiles] depending on validity or lack of normality assumptions. Overall comparisons across groups were based on unpaired Student's t-test for continuous variables (or Mann-Whitney U-test and Kruskal-Wallis test in case of significant departures from normality assumptions, namely, $P<0.05$ on Kolmogorov-Smirnov or Shapiro-Wilks tests) and chi-squared or Fisher's exact test for categorical variables (with the latter used when the expected cell count was <5). To determine the independent predictors of ISA, OCT and histopathological variables with a P-value <0.05 on univariate analysis were entered into a multivariate logistic regression model. A 2-tailed P-value <0.05 was considered statistically significant for hypothesis testing, with P unadjusted for multiplicity reported throughout.

Results

Of 140 STEMI patients enrolled in the OCTAVIA trial, 114 patients with 114 stented lesions had serial OCT data analyzable at all prespecified time points (Figure 3). The mean length of the analyzed target segment was 44.2±11.5 mm. Clinical and procedural characteristics of the study population are reported in Table S1. The mean age of the study population was 65.9±10.8 years, and 51% of patients were male. Median time from symptoms onset to the catheterization laboratory was 2.4 (interquartile range (IQR) 1.7–3.5) h. Manual thrombectomy was performed in 97 (85%) and GP IIb/IIIa inhibitors were used in 51 (45%) of the 114 patients. The incidence of acute, resolved, persistent and late-acquired ISA is summarized in Figure 3.

Acute ISA

Of 114 stented lesions, 82 (71.9%) had at least 1 malapposed strut at post-implant and Stents with ≥5% of malapposed struts were observed in 48.2% of cases (Figure 3). Acute ISA

Table 2. OCT Findings in Lesions With and Without Acute, Resolved, or Late-Acquired ISA

Variable	Acute ISA (+) (n=82)	Acute ISA (–) (n=32)	P value	Persistent ISA (n=46)	Resolved ISA (n=36)	P value	LAISA (+) (n=39)	LAISA (–) (n=75)	P value
Culprit plaque assessment									
Etiology			0.16			0.52			0.15
Rupture	42 (51.2)	14 (43.8)		22 (47.8)	20 (55.6)		21 (53.8)	35 (46.7)	
Erosion	15 (18.3)	11 (34.4)		8 (17.4)	7 (19.4)		10 (25.6)	16 (21.3)	
Spontaneous Dissection	2 (2.4)	0 (0)		1 (2.2)	1 (2.8)		1 (2.7)	1 (1.3)	
Indeterminate	23 (28.0)	7 (21.9)		15 (32.6)	8 (22.2)		7 (17.9)	23 (30.7)	
Rupture length, mm	1.8 [1.2–2.9]	2.0 [1.6–3.1]	0.49	1.7 [1.20–2.45]	1.9 [1.05–3.8]	0.49	2.4 [1.2–4.1]	1.6 [1.2–2.2]	0.04
Plaque constituents at MLA									
Lipidic, %	73.7±34.0	70.3±29.4	0.45	71.5±35.6	76.4±32.4	0.52	75.7±31.7	71.2±33.4	0.49
Calcified, %	6.9±16.7	3.9±14.0	0.43	7.1±17.2	6.7±16.6	0.92	6.4±15.9	5.9±16.4	0.87
Fibrotic, %	12.1±23.8	20.3±28.7	0.16	13.8±25.2	10.0±22.0	0.47	9.6±21.2	16.9±27.2	0.14
Normal, %	7.3±17.6	5.5±13.8	0.79	7.6±18.9	6.9±24.4	0.89	8.3±24.6	6.0±16.4	0.54
Thrombus presence	78 (95.1)	27 (84.4)	0.11	43 (93.5)	35 (97.2)	0.62	38 (97.4)	67 (89.3)	0.16
Thrombus components			0.24			1.00			0.01
White thrombus	35 (44.8)	10 (37.0)		19 (44.2)	16 (45.7)		10 (26.3)	35 (52.2)	
Red/mixed thrombus	43 (55.1)	17 (63.0)		24 (55.8)	19 (54.3)		28 (73.7)	32 (47.8)	
Target segment assessment									
Plaque constituents									
Lipidic, %	36.4±17.6	29.8±14.0	0.04	36.3±18.3	36.7±17.0	0.93	35.4±16.0	34.8±17.4	0.87
Calcified, %	6.9±10.1	4.2±5.0	0.26	8.0±12.1	5.5±6.6	0.28	6.2±8.5	6.3±9.5	0.93
Fibrotic, %	30.2±15.6	35.7±13.1	0.14	28.6±16.2	32.3±14.8	0.29	32.8±14.4	31.4±16.2	0.65
Normal, %	26.5±20.2	30.3±18.1	0.16	27.1±19.2	25.5±21.7	0.71	25.6±21.1	27.5±17.2	0.63
No. of TCFA	1.5 [0.8–3]	1.0 [0.0–2.0]	0.04	1.0 [0.0–2.0]	2.0 [1.0–3.0]	0.05	2.0 [1.0–3.0]	1.0 [0.0–2.0]	0.03
Total length of TCFA, mm	2.1 [0.3–5.1]	1.4 [0.0–4.1]	0.13	1.8 [0.0–5.0]	2.6 [1.25–5.7]	0.13	3.2 [0.8–6.0]	1.7 [0.0–3.8]	0.01

Data are presented as n/N (%), mean±standard deviation, or median [1st–3rd quartile]. MLA, minimal lumen area; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma. Other abbreviations as in Table 1.

equally involved the stent body and the edges. Compared with lesions without ISA, acute ISA was more likely to occur in larger vessels (angiographic RVD 2.7 (2.4–3.1) vs. 2.5 (2.1–2.9) mm, P=0.02, and reference vessel area by OCT of 7.1 (5.6–9.9) vs. 5.8 (4.7–7.1) mm^2, P=0.01) and in vessels with significantly higher lipid content of the target segment (36.4±17.6% vs. 29.8±14.0%, P=0.04) (Tables 1–3). Histopathological analyses of aspirated thrombus and inflammatory serum biomarkers did not show any significant difference between patients with and without acute ISA.

Persistent ISA

Of the 82 lesions with acute ISA, 46 (56.1%) had persistent ISA at follow-up (Figure 3), with median ISA areas and volumes of 0.2 mm^2 (IQR 0.1–0.3) and 2.1 mm^3 (IQR 1.0–7.4), respectively. Stents with ≥5% of malapposed struts were observed in 28 (38.9%) of cases. Persistent ISA was mostly (76.1%) located at the stent edges. No differences in the angiographic and procedural characteristics were noted between lesions with persistent vs. resolved ISA (Table 1). By OCT, similar culprit lesion morphologies and atherothrombotic vessel components were also observed between groups (Table 2). However, the stent expansion index at implant was significantly lower in persistent vs. resolved ISA (79.6% (63.6–99.4%) vs. 88.1% (80.0–101.0%), P=0.04). In addition, persistent ISA was associated with longer distance, longer segment, larger area and volume of ISA at the index procedure (Table 3). Further, receiver-operating curve analyses indicated a length of consecutive malapposed struts >4.2 mm as the best cut-off value to discriminate between the likelihood of having persistent vs. resolved ISA at follow-up (area under the curve=0.69, P=0.004, 95% confidence interval (CI) [0.57–0.81], sensitivity=80.6%, specificity=63.0%). Interestingly, 43.9% of the acute ISA lesions had a length of consecutive malapposed struts >4.2 mm.

Late-Acquired ISA

A total of 39 (34.2%) lesions developed late-acquired ISA at 9-month follow-up (Figures 3,4). The median ISA areas and volumes were 0.3 [IQR 0.1–0.4] mm^2 and 3.3 [IQR 1.1–9.6] mm^3, respectively at 9-month follow-up OCT (Table 3). Late-acquired ISA was mainly (82%) located at the stent body and developed more frequently in stented lesions with a lower rate of post-dilation (43.6% vs. 65.3%, P=0.02) (Table 1). Notably, lesions with late-acquired ISA had a longer length of underlying plaque rupture (2.4 (IQR 1.2–4.1) vs. 1.6 (IQR 1.2–2.2) mm, P=0.04) and more red/mixed thrombus (71.8% vs. 42.7%, P=0.01) at baseline OCT compared with lesions without late-acquired ISA (Table 2). Similarly, the histopathological analysis of thrombus aspirates revealed larger thrombus volume and more organized thrombi in lesions with late-acquired ISA (Table 4). Patients with late-acquired ISA also had higher serum levels of MPO and a trend to higher ECP at 9-month follow-up (Table 4).

Table 3. OCT Morphometric Analysis at Baseline in Lesions With and Without Acute, Persistent or Late-Acquired ISA

Variable	Acute ISA (+) (n=82)	Acute ISA (–) (n=32)	P value	Persistent ISA (n=46)	Resolved ISA (n=36)	P value	LAISA (+) (n=39)	LAISA (–) (n=75)	P value
At stent implantation									
Reference vessel area, mm^2	7.1 [5.6–9.9]	5.8 [4.7–7.1]	0.01	8.5 [5.8–11.4]	6.7 [5.2–8.5]	0.04	8.3 [6.1–12.0]	6.3 [5.2–8.5]	0.19
Vessel lumen volume, mm^3	264.6 [207.7–348.8]	221.8 [179.0–286.9]	0.04	283.5 [188.7–373.9]	248.0 [222.2–325.4]	0.42	284.9 [206.9–370.1]	246.0 [175.8–309.0]	0.03
Analyzed stent length, mm	23.5 [18.4–32.2]	21.0 [17.2–29.0]	0.07	22.9 [18.2–32.2]	27.0 [19.1–34.6]	0.33	22.4 [17.8–33.4]	23.2 [18.0–31.6]	0.96
Minimum stent area, mm^2	6.4 [5.0–8.6]	5.1 [4.2–6.5]	0.02	6.8 [5.1–9.2]	5.7 [4.5–7.6]	0.07	6.1 [4.9–8.8]	5.9 [4.4–7.5]	0.11
Stent expansion index, %	86.7 [70.4–100.9]	93.2 [82.0–103.6]	0.13	79.6 [63.6–99.4]	88.1 [80.0–101.0]	0.04	83.8 [76.1–86.7]	83.0 [76.9–88.6]	0.86
Mean protruding area, mm^2	0.4 [0.2–0.5]	0.4 [0.2–0.6]	0.20	0.3 [0.2–0.5]	0.3 [0.2–0.4]	0.80	0.4 [0.2–0.6]	0.3 [0.2–0.4]	0.09
% Struts with ISA	8.7 [3.9–14.1]	–	–	11.1 [5.5–19.0]	4.5 [2.9–9.2]	<0.001	–	–	–
Maximum ISA distance, μm	400 [200–500]	–	–	400 [300–600]	300 [200–300]	<0.001	–	–	–
Maximum ISA length, mm	3.6 [2.2–6.0]	–	–	4.8 [2.4–6.1]	2.4 [1.2–3.6]	<0.001	–	–	–
ISA area, mm^2	0.2 [0.1–0.4]	–	–	0.3 [0.1–0.6]	0.1 [0.1–0.2]	<0.001	–	–	–
ISA volume, mm^3	4.4 [1.9–8.3]	–	–	6.1 [3.1–11.8]	2.7 [1.1–5.4]	<0.001	–	–	–
9-month follow-up									
Minimum stent area, mm^2	–	–	–	8.4 [0.2–11.0]	6.4 [5.5–8.06]	0.01	7.02 [5.4–9.3]	6.6 [5.3–8.6]	0.07
% Struts with ISA	–	–	–	3.9 [1.4–9.3]	–	–	6.4 [2.1–11.5]	2.6 [0.7–4.8]	<0.001
Maximum ISA distance, mm	–	–	–	300 [200–500]	–	–	400 [200–500]	200 [100–500]	0.05
Maximum ISA length, mm	–	–	–	1.8 [0.6–3.3]	–	–	2.8 [0.6–5.4]	0.6 [0.6–1.8]	<0.001
ISA area, mm^2	–	–	–	0.2 [0.1–0.3]	–	–	0.3 [0.1–0.4]	0.1 [0.02–0.2]	<0.001
ISA volume, mm^3	–	–	–	2.1 [1.0–7.4]	–	–	3.3 [1.1–9.6]	0.2 [0.0–1.4]	<0.001
Mean neointimal thickness, μm	–	–	–	67.7 [44.3–95.9]	110.6 [93.9–138.8]	<0.001	56.8 [35.5–77.9]	75.2 [53.8–113.3]	<0.001
% Net volume obstruction	–	–	–	7.4 [4.4–10.7]	13.4 [9.5–17.2]	<0.001	6.4 [3.5–10.3]	13.2 [7.79–18.6]	<0.001
Uncovered struts	–	–	–	14.3 [7.6–28.4]	4.4 [1.6–9.9]	<0.001	18.0 [12.4–37.0]	11.2 [5.9–21.0]	<0.001
Frames with >30% uncovered struts	–	–	–	18.5 [10.2–44.7]	5.2 [0.0–14.3]	<0.001	21.1 [6.6–50.0]	5.8 [0.00–15.8]	<0.001

Data are presented as n/N (%), mean±standard deviation, or median [1 st–3rd quartile]. Abbreviations as in Tables 1,2.

Predictors of ISA

In the multivariate analysis, larger lumen vessel (odds ratio (OR) 1.2; 95% CI [1.0–1.1]; P=0.03), the presence of thrombus before stent implantation (OR 5.5; 95% CI [1.1–26.9]; P=0.04) and higher lipid content in the target segment (OR 1.3; 95% CI [1.0–1.5]; P=0.04) were independently associated with acute ISA. Larger ISA volume immediately after stent implantation was also independently associated with persistent ISA (OR 1.4; 95% CI [1.2–1.6]; P<0.001). Longer length of plaque rupture (OR 1.7; 95% CI [1.1–2.8]; P=0.02) and the presence of red/mixed thrombus before stent implantation (OR 3.7; 95% CI [1.0–13.3]; P=0.05) were also independently associated with late-acquired ISA.

Clinical Outcomes

No significant differences in major adverse cardiac and cerebrovascular events and stent thrombosis at 24-month follow-up were observed between patients with and without ISA at 9-month follow-up (Table S2).

Discussion

This prespecified analysis of the OCTAVIA trial reports for the first time on the effect of different culprit plaque morphologies and infarct-related artery atherothrombotic components on ISA following p-PCI with EES in STEMI. The main findings were: (1) the atherothrombotic components of the plaque responsible for STEMI play a significant role in the onset of acute and late-acquired ISA; (2) the size and the lon-

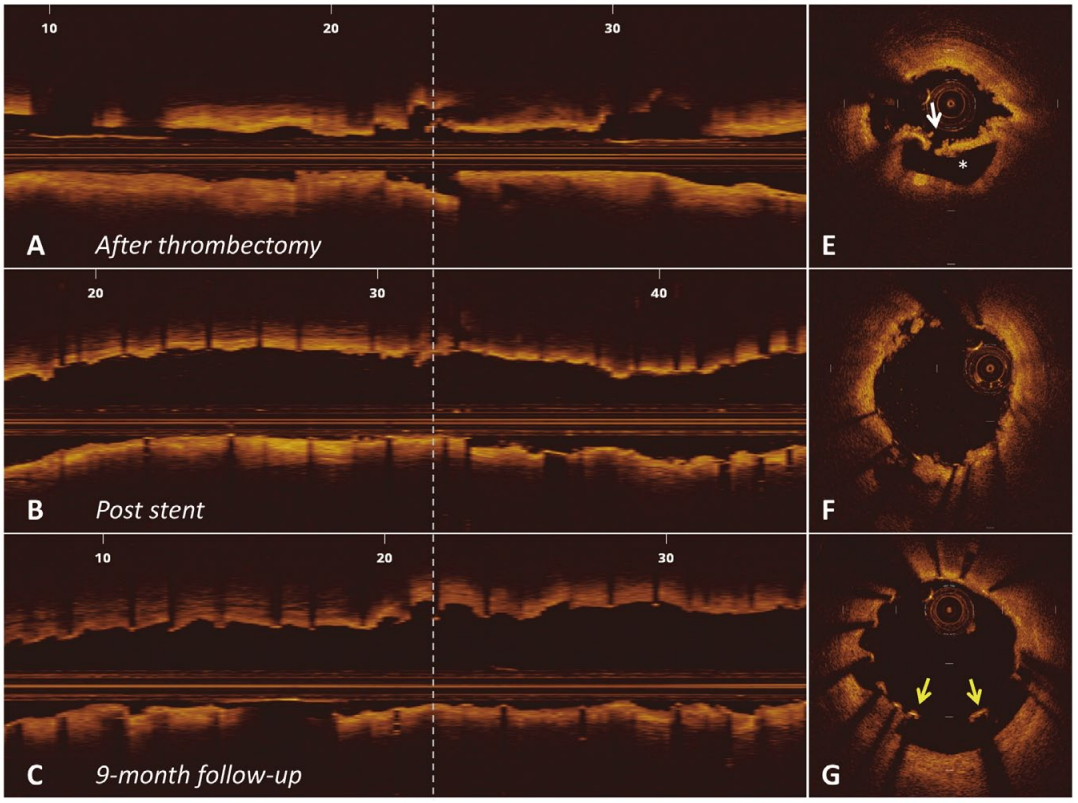

Figure 4. Example of late-acquired incomplete stent apposition. (**A**–**C**) Longitudinal views after thrombectomy, post-stenting and at 9-month follow-up, respectively. (**E**–**G**) Cross-sectional views after thrombectomy, post-stenting and at 9-month follow-up, respectively. The vertical dashed line in the longitudinal views indicates the location of the cross-sectional images. Plaque rupture (white arrow) with a large cavity (*), remnants of the thin cap and white thrombus fragments are shown (**E**). Corresponding longitudinal and cross-sectional views illustrate complete stent apposition to the vessel wall and debris of the original plaque behind the struts (**B**,**F**). The struts in the case of late-acquired ISA (LAISA) (yellow arrow) at 9-month follow-up are shown at the stent body corresponding exactly to site of the original culprit plaque rupture (**C**,**G**).

gitudinal extent of malapposed struts immediately after stenting significantly predict the persistency or resolution of ISA; and (3) despite the high frequency of malapposed struts detected by OCT, ISA observed with current-generation EES has a limited extension and its clinical meaning remains undefined.

Incidence, Characteristics and Effect of ISA

ISA detected by OCT is nearly a ubiquitous finding in patients undergoing p-PCI, even with current-generation DES.[1,2] We observed acute, persistent and late-acquired incomplete apposition of at least 1 stent strut in 71.9%, 56.1% and 34.2% of patients, respectively. Still, when the more meaningful threshold of ≥5% of malapposed struts was considered, ISA was detected acutely in 48.2% of cases and in 35.9% at 9 months. Not surprisingly, the average extent of ISA, expressed as maximum distance, area and volume of ISA, was limited in dimensions at all time points and apparently not associated with adverse events at 24 months.[14]

Mechanisms and Determinants of ISA

Pathology studies have demonstrated a greater prevalence of ISA in thrombotic lesions.[15] Using OCT, Kubo et al confirmed in vivo that ISA is more likely to occur when a stent covers thin-cap fibroatheroma, ruptured plaque, and lesions with thrombus or high lipid content.[16] We expanded these observations to STEMI patients undergoing p-PCI with current-generation EES. In the present study, acute ISA developed more frequently in larger vessels, with greater thrombus burden and higher lipid content at the target segment. Despite manual thrombectomy being used in the majority of patients in OCTAVIA and judged effective from an angiographic standpoint, a 5.5-fold increased risk of acute ISA was observed in stented lesions with OCT-detected residual thrombus. These results are consistent with OCT studies that recently assessed manual thrombectomy in patients undergoing p-PCI, where similar high rates of remaining thrombus and no substantial improvement in the mean flow area were reported after stenting with thrombus aspiration compared with stenting alone.[17,18] Conversely, acute ISA, especially in the vessels with larger reference lumen area, was frequently observed at stent edges without any plaque in the present study. This finding suggested that acute ISA in situations in which there is difficulty in obtaining fully apposed struts can be independent of plaque morphology or residual thrombus. Further, the present study suggested a potential relationship between culprit plaque char-

Table 4. Histologic Assessment of Aspirated Thrombi and Serum Inflammatory Biomarkers Evaluation in Lesions With and Without Late-Acquired ISA

Variable	LAISA (+) (n=39)	LAISA (–) (n=75)	P value
Analyzed thrombus materials	23 (34.8)	43 (65.2)	
Histopathological analysis			
Thrombus volume, mm^3	10.0 [5.0–25.0]	4.0 [2.0–15.0]	0.04
Thrombus age			0.03
Early (<1 day)	5 (21.7)	22 (47.8)	
Organized (≥1 day)	18 (78.3)	24 (52.2)	
Platelets present	23 (100.0)	43 (100.0)	
Plaque material	13 (56.5)	20 (46.5)	0.30
Immunohistochemical analysis			
CD68, cells/5HPF	27.5 [15.0–50.0]	15.0 [10.0–30.0]	0.13
% Eosinophils	0.00	0.00	
IL5, cells/5HPF	1.0 [0.0–1.0]	0.0 [0.0–0.0]	0.03
MPO, cells/5HPF	44.0 [30.0–111.0]	38.5 [25.3–76.3]	0.25
Serum biomarker analysis			
hs-CRP, mg/L			
Index	1.7 [0.7–3.7]	1.9 [0.9–3.9]	0.41
9-month	0.9 [0.5–2.1]	1.0 [0.4–2.2]	0.96
MPO, ng/ml			
Index	837 [290–1,725]	550 [279–1,311]	0.26
9-month	374.6 [151.3–541.6]	219.0 [50.8–384.1]	0.02
ECP, mg/L			
Index	5.2 [3.0–8.6]	4.5 [2.4–9.7]	0.77
9-month	6.0 [2.1–16.2]	2.9 [2.0–10]	0.07
TBX_2, pg/ml			
Index	101.8 [63.3–255.0]	97.7 [57.7–218.8]	0.69
9-month	156.3 [71.7–263.5]	175.7 [95.7–229.1]	0.83

Data are presented as n/N (%), mean ± standard deviation, or median [1 st–3rd quartile]. CD, cluster of differentiation; ECP, eosinophil cationic protein; HPF, high-power field; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MPO, myeloperoxidase; TBX_2, thromboxane B_2. Other abbreviations as in Table 1.

acteristics and thrombus components with the onset of late-acquired ISA. Lesions developing late-acquired ISA were associated with longer ruptured plaque at the culprit site and larger and more organized thrombus. In the present study, similarly to prior intravascular ultrasound investigations, late-acquired ISA was mainly located at the stent body, suggesting lipid-rich plaque resorption and/or later thrombus fragments dissolution as contributing factors involved in its generation.[3–5] Intriguingly, in patients with late-acquired ISA, we observed a significant elevation of serum MPO levels and a trend to higher ECP values at 9-month follow-up compared with patients without. Late-acquired ISA has been previously identified as a marker of local ongoing inflammation after 1st-generation DES implantation.[3,4] However, whether persistent elevation of systemic MPO and ECP might have a causative role in the development of late-acquired ISA cannot be ascertained from the present study, because these parameters were not found to be significant predictors after adjustment for potential confounders.

Sequential Changes of ISA

The culprit lesion and vessel features did not play a major role in ISA persistency. Consistent with prior OCT studies conducted in different patient cohorts, persistent ISA after p-PCI was mainly related to the acute extent of ISA and suboptimal stent expansion at implantation.[2,5,19] Compared with resolved ISA, persistent ISA had a longer maximum ISA distance, and larger area and volume of ISA at the index OCT. The volume of ISA emerged as an independent factor implicated in the persistence or resolution of ISA. This suggests that only stented lesions with a large volume of ISA should be accounted and corrected as a possible source of very late adverse events.

Strategies to Reduce ISA in p-PCI

Considering the result that the presence of thrombus before stent implantation and red/mixed thrombus were substantial contributing factors to acute ISA and late-acquired ISA, respectively, it is likely that complete removal of thrombus could be effective in reducing both acute and late-acquired ISA. However, previous OCT studies demonstrated that manual thrombectomy during PCI was not associated with a significantly smaller extent of acute ISA[17] and allowed only incomplete removal of thrombus[18] in patients with STEMI. Self-expanding stents have been recently proposed as a possible strategy to avoid ISA in STEMI.[20] Moreover, in the present study, lesions with persistent ISA had lesser stent expansion than in lesions with resolved ISA. Despite some concerns of distal embolization, more efficient initial thrombus removal followed by optimal stent sizing could be an effective treatment strategy for reducing persistent or late-acquired ISA.[21] OCT, with its high sensitivity in detecting and

quantifying thrombus and accurate lumen measures might optimally guide this interventional strategy.[22]

Study Limitations

Despite its high level of accuracy in characterizing coronary plaques, the OCT signal cannot deeply penetrate tissues in the presence of lipid plaques, leading to high scattering and rapid light attenuation.[23] This property precludes quantification of positive vessel remodeling, a recognized mechanism responsible for late-acquired ISA. Moreover, the alignment procedure for corresponding OCT cross-sections at different time points, despite the use of fiduciary landmarks, has an unavoidable degree of inaccuracy. Manual thrombectomy was performed before OCT imaging in patients presenting with Thrombolysis In Myocardial Infarction flow grade 0–1 or filling defect. The possibility of modifying the plaque morphology by thrombectomy catheter cannot be entirely ruled out. Furthermore, there is a possibility that the rupture length was underestimated because of residual thrombus. The lack of histopathology and serum inflammatory biomarkers assessment in some of the patients is limiting the value of the relative analyses. Finally, this study was underpowered to show any difference in event rates between patients with and without ISA. Thus, the link between ISA and long-term outcomes cannot be properly evaluated.

Conclusions

In STEMI patients undergoing p-PCI with EES, culprit plaque and vessel atherothrombotic components play a role in the onset of acute and late-acquired ISA. Thrombotic lesions anticipate acute ISA, whereas the length of the underlying ruptured plaque and remnants of red/mixed thrombus are independently associated with late-acquired ISA. Persistent ISA reflects the volume of ISA post-procedure. Overall, ISA with current-generation EES was found to be limited in extent and not associated with adverse clinical outcomes up to 2 years.

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Disclosures and Conflicts of Interest

F.S. reports receiving consulting fees from Abbott Vascular, Astra Zeneca, Eli Lilly, Medtronic and St. Jude Medical and receiving speaker's honoraria fees from Astra Zeneca, Biosensors Edwards, Boston Scientific, Eli Lilly, St. Jude Medical and Terumo; R.G. reports receiving consulting fees from Alvimedica, Terumo and Volcano and receiving speaker's honoraria fees from Abbott Vascular and St Jude Medical; F.B. reports receiving speaker's honoraria fees from Medtronic, St. Jude Medical and Abiomed; G.C. reports receiving consulting fees from Menarini, Astra Zeneca and Boehringer Ingelheim; L.V. reports receiving consulting fees from St. Jude Medical; G.B.-Z. reports receiving consulting fees from Abbott Vascular and St. Jude Medical; G.G. reports receiving consulting fees from Boston Scientific, St. Jude Medical; C.B., K.S., K.K., M.C., H.Y., G.N., E.L. report no conflicts of interest.

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Supplementary Files

Supplementary File 1

Figure S1. OCT criteria used to align corresponding OCT cross-sections obtained before, after stenting and at 9-month follow-up.

Table S1. Baseline clinical and procedural characteristics

Table S2. Clinical outcomes at 2 years in patients with and without ISA at 9 months

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-15-1140