Clinical Impact of Suboptimal Stenting and Residual Intrastent Plaque/Thrombus Protrusion in Patients With Acute Coronary Syndrome

The CLI-OPCI ACS Substudy (Centro per la Lotta Contro L'Infarto-Optimization of Percutaneous Coronary Intervention in Acute Coronary Syndrome)

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Background—Clinical consequences of optical coherence tomographic (OCT) high-definition visualization of plaque/stent structures in acute patients remain undefined. In this retrospective substudy, we assessed the prognostic impact of postprocedural culprit lesion OCT findings in patients with acute coronary syndrome undergoing percutaneous coronary intervention.

Methods and Results—In the CLI-OPCI (Centro per la Lotta Contro L'Infarto-Optimization of Percutaneous Coronary Intervention) database collecting cases from 5 independent OCT-experienced centers, we retrospectively analyzed postprocedural OCT findings in acute coronary syndrome patients and explored its possible impact (specifically that of residual intrastent plaque/thrombus protrusion) on outcome. From 2009 to 2013, 507 patients (588 lesions) were evaluated. Patients experiencing device-oriented cardiovascular events showed more frequently the features of suboptimal stent implantation defined as the presence of significant residual intrastent plaque/thrombus protrusion (hazard ratio [HR], 2.35; $P<0.01$), in-stent minimum lumen area (MLA) <4.5 mm^2 (HR, 2.72; $P<0.01$), dissection >200 μm at distal stent edge (HR, 3.84; $P<0.01$), and reference lumen area <4.5 mm^2 at either distal (HR, 6.07; $P<0.001$) or proximal (HR, 8.50; $P<0.001$) stent edges. Postprocedural OCT assessment of treated culprit lesion revealed at least one of these parameters in 55.2% of cases, with an associated increased risk of device-oriented cardiovascular events during follow-up (17.9% versus 4.8%; $P<0.001$). Both the presence of at least one of these parameters (HR, 3.69; $P=0.002$) and the residual intrastent plaque/thrombus protrusion (HR, 2.83; $P=0.008$) were confirmed as independent predictors of device-oriented cardiovascular events.

Conclusions—In this retrospective study of acute coronary syndrome patients undergoing percutaneous coronary intervention, a composite of OCT-defined suboptimal stent implantation characteristics at the culprit lesion and residual intrastent plaque/thrombus protrusion was associated with adverse outcome. (***Circ Cardiovasc Interv*. 2016;9:e003726. DOI: 10.1161/CIRCINTERVENTIONS.115.003726.)**

Key Words: acute coronary syndrome ■ percutaneous coronary intervention ■ prognosis ■ registries ■ stents

Plaque rupture and thrombus formation play a key role in the pathogenesis of acute coronary syndrome (ACS).[1] Moreover, in this clinical setting, percutaneous coronary intervention (PCI) can be hampered by distal embolization of plaque debris and thrombus components, the main determinants of the no-reflow phenomenon.[2] The introduction of

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WHAT IS KNOWN

- Recent studies showed optical coherence tomography (OCT) metrics that were related to clinical outcome after coronary intervention with stenting.
- Nevertheless, clinical consequences of these OCT findings, including plaque/thrombus intrastent prolapse, in the setting of acute coronary syndrome remain undefined.

WHAT THE STUDY ADDS

- This study confirms the OCT usefulness during percutaneous coronary intervention to identify acute coronary syndrome patients at increased risk of adverse outcome. Indeed, residual intrastent plaque/thrombus protrusion, in-stent minimum lumen area <4.5 mm^2, residual dissection at the distal stent edge, and reference lumen area <4.5 mm^2, at both stent edges, were observed in half of patients and were associated to an increased risk of adverse cardiac events.
- The adequate treatment of OCT-defined suboptimal stent deployment remains to be investigated.

optical coherence tomography (OCT), a high-resolution intracoronary imaging technique, has enabled an improved characterization of culprit plaques (especially thrombus and lipid detection) and has allowed the identification of some stent deployment parameters correlating with major adverse coronary events occurrence.[3–7] In particular, the CLI-OPCI (Centro per la Lotta Contro L'Infarto-Optimization of Percutaneous Coronary Intervention) registries contributed to the definition of suboptimal stent implantation and its negative impact on outcome and speculated on the clinical use of OCT assessment.[6,7] Preliminary data have suggested that intrastent residual thrombus might be associated with an increased risk of myocardial infarction (MI) recurrence (particularly periprocedural MI) and stent thrombosis.[8–10] However, the true clinical significance of residual intrastent plaque/thrombus burden remains debated.[11,12]

In this study, we sought to explore, in a large ACS patient population, the correlation between suboptimal stent deployment at the culprit lesion sites and clinical outcomes with the specific goal to assess the role of residual intrastent plaque/thrombus protrusion among the already validated criteria of suboptimal stent deployment.[7]

Methods

Study Design

This study was carried on in the context of the CLI-OPCI project aiming to assess the feasibility and usefulness of an OCT-guided approach during PCI.[6,7] All centers joining the registry used a dedicated database for data entry, explicit definitions for baseline and procedural characteristics (ie, angiographic features). and scheduled follow-up (by means of direct visit or phone interview).

In this substudy of the CLI-OPCI II registry, all patients with ACS diagnosis (unstable angina and acute MI with or without ST-segment–elevation),[13] undergoing adequate postprocedural frequency domain OCT assessment of the treated culprit lesions, including the whole stent length and the proximal and distal reference segments, were considered.[14–16] For the study purpose, only final OCT findings were considered, regardless of original OCT screening indication or practical consequences (eg, stent postdilation) deriving from its use during the procedure; in particular, no formal indication for treatment of OCT findings was adopted. Written informed consent was obtained for the index procedure, for the phone/direct follow-up visit, and anonymous data management; ethical approval was waived in the light of the observational retrospective design.

As the primary objective of the study, we explored the clinical consequences of suboptimal stent deployment defined according to the quantitative OCT criteria; in particular, the impact of residual intrastent plaque/thrombus protrusion on outcome was appraised. The rate of device-oriented cardiovascular events (DoCE)—a composite of cardiac death, target vessel–related MI (including periprocedural MI, defined as creatine kinase muscle and bone [CK-MB] >3× the upper limit of normal),[17] and target lesion revascularization—represented the primary end point of the study. All outcomes were defined according to the Academic Research Consortium recommendations[18] and adjudicated in a blinded fashion by a central clinical event committee at certified central core laboratory (Rome Heart Research, Rome, Italy).

The CLI-OPCI registry has been sponsored by the Centro per la Lotta Contro L'Infarto-Optimization of Percutaneous Coronary; and thus, no extramural funding was used to support this work.

Procedures

PCIs were performed using standard techniques and catheters via femoral or radial approach according to the operator/center common practice. Coronary angiography was carried on according to the validated standards. All patients were pretreated with 325 mg aspirin and loaded with 600 mg clopidogrel, 60 mg of prasugrel, or 180 mg of ticagrelor. Intraprocedural unfractionated heparin or bivalirudin was administered to obtain an intraprocedural activated clotting time of 250 to 300 s, whereas adjunctive pharmacological therapy (ie, glycoprotein IIb/IIIa inhibitors) was left to the operator's choice.

At discharge, dual antiplatelet therapy was recommended for at least 12 months; patients were followed by means of scheduled direct visits (generally at 1 and 6 months) and phone contacts (after 12 months). In case of any adverse event or new hospitalization, additional visits were planned; source documents were obtained and examined in detail by the clinical event committee that adjudicated each event to a specific culprit lesion.

Imaging Measurements and Definitions

All images were analyzed off-line at a certified core laboratory (Rome Heart Research) by readers blinded to the clinical outcome. A computer-assisted system and an automated edge detection algorithm (MEDIS, Leiden, The Netherlands) were adopted for quantitative coronary analysis assessment.[19] OCT was acquired by means of the FD C7 XR or OPTIS system (both St. Jude Medical, St. Paul, MN) with a standardized nonocclusive technique.[3,14] Importantly, all OCT acquisitions selected for core laboratory reading were performed at the end of the PCI procedure.

Conventional definitions were derived from expert consensus OCT documents,[3,20] whereas applied quantitative OCT definition of suboptimal stent implantation was derived from the CLI-OPCI registries.[6,7] The following quantitative OCT parameters were considered:

1. Edge dissection: the presence of a linear rim of tissue with a maximal width ≥200 μm and a clear separation from the vessel wall or underlying plaque that was adjacent (<5 mm) to a stent edge.[3,15]
2. Reference lumen narrowing: lumen area <4.5 mm^2 in the presence of significant residual plaque adjacent to stent edges.[15]
3. Malapposition: stent-adjacent vessel lumen distance >200 μm.[15,21,22]
4. In-stent MLA <4.5 mm^2.[15]

5. Minimum stent area (MSA) <4.5 mm^2 (assessed along the entire length of the stent and not necessarily corresponding to the MLA site).
6. Residual stenosis: in-stent MLA <70% of the average reference lumen area.[15]
7. Intrastent plaque/thrombus protrusion: tissue ≥500 μm in thickness prolapsing between stent struts into the vessel lumen.[3,7,21,23]

Definition of suboptimal OCT stent implantation required the presence of at least one of the OCT findings that were significantly associated with DoCE in the univariate analysis (Figure 1).

Statistical Analysis

Continuous variables were reported as means (±SD) or median (first–third quartile) in case of normal or skewed distribution; discrete variables were reported as percentages. Student *t*, Mann–Whitney *U*, χ^2, and Fisher exact tests were applied for bivariate analyses when appropriate. Correlation analysis was performed to determinate the association between MLA and MSA using Pearson correlation ρ test. The outcome predictive accuracy of intrastent plaque/thrombus protrusion was evaluated with the receiver operating characteristic curve, and highest Youden index (*J*), representing the maximum potential effectiveness, was used to confirm the selected cut-off.[24,25] Combined adverse events were evaluated on a per-patient hierarchical basis and summarized as Kaplan–Meier estimates. All variables in Tables 1 and 2 were tested for bivariate association with DoCE and if nominally significant (P<0.05) were simultaneously forced into a Cox regression model to identify independent outcome predictors and to calculate their adjusted hazard ratios (HRs) with associated 95% confidence intervals (CIs). The Cox regression model included the following variables: left ventricular ejection fraction, diabetes mellitus, coronary artery disease family history, chronic kidney disease, non–ST-segment–elevation MI (non-STEMI) diagnosis, multivessel disease, previous MI, in-stent restenosis, ostial lesion treatment, bare metal stent implantation, and suboptimal final OCT result. Finally, the specific impact of intrastent plaque/thrombus protrusion was assessed using a further Cox regression model, including this feature separately from all other OCT parameters.

A 2-tailed, P value <0.05 was established as the level of statistical significance for all tests. All statistical analyses were performed using SPSS-PASW 22.0 (IBM, Armonk, NY).

Results

From 2009 to 2013, a total of 507 consecutive patients with ACS diagnosis and poststenting OCT assessment of the identified culprit lesions were retrospectively enrolled from 5 independent high-volume and OCT-experienced centers joining the CLI-OPCI projects.

Tables 1 and 2 summarize the clinical and procedural characteristics of the study population. Median patient age was 63 years (quartiles 55–72 years) with 19.7% females. All patients had an acute clinical presentation, including acute STEMI in 52.3%, non-STEMI in 16.8%, and unstable angina in 31.0%.

Treated culprit lesions were located in the left main in 3.1% of cases, left anterior descending artery in 52.9%, left circumflex artery in 18.7%, right coronary artery in 25.0%, and graft conduit in 0.3%. Most of the lesions showed a complex profile (Ellis class B2/C 73.1%)[26]; a strategy of prestent thrombectomy was adopted in 48.0% of STEMI patients, whereas direct stenting was performed in only 27.4% of cases. About half of the patients had multivessel disease involvement and were mostly treated with drug-eluting stents or bioresorbable vascular scaffolds (68.0% and 4.6% of lesions, respectively); multiple overlapping stents were implanted in 20.6%, whereas high-pressure stent postdilation was performed in 48.0% of cases. Optimal angiographic success, defined as residual stenosis <30% and final Thrombolysis in Myocardial Infarction 3 flow, was obtained in 89.1% of patients with a periprocedural MI rate of 2.4%.

OCT Analysis

OCT assessment was performed in 588 stented lesions and revealed suboptimal stent implantation findings in 55.2% of the patients. In particular, OCT disclosed in-stent MLA <4.5 mm^2 in 22.1%, MSA <4.5 mm^2 in 21.1%, residual stenosis (MLA <70% of the reference lumen) in 24.3%, intrastent plaque/thrombus protrusion >500 μm in 32.1%, malapposition in 48.0%, edge dissection in 13.4%, and reference lumen narrowing in 7.7% of the stented lesions (Table 3).

A high correlation between MLA and MSA was observed (R^2=0.933); but in 24/130 (18.5%) lesions, we observed an MSA >4.5 mm^2 in the presence of an MLA <4.5 mm^2; these cases, representing patients with greater atherothrombus prolapse, showed a mean intrastent tissue area percentage of 18.0±12.3%. On the other hand, there were only 5/124 (4.0%)

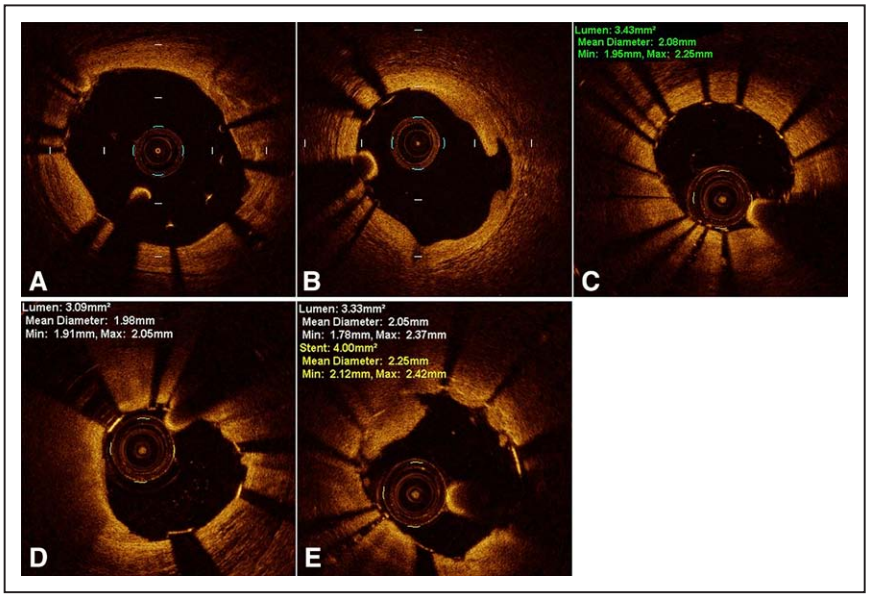

Figure 1. Optical coherence tomographic (OCT) criteria identifying suboptimal OCT stent deployment. **A**, Stent malapposition (stent-adjacent vessel lumen distance >200 μm); (**B**) stent edge dissection (tissue rim with a width ≥200 μm and a clear separation from the vessel wall or underlying plaque); (**C**) in-stent minimum lumen area <4.5 mm^2; (**D**) reference lumen narrowing (lumen area <4.5 mm^2 in the presence of significant plaque adjacent to stent edges); (**E**) intrastent plaque/thrombus protrusion (tissue prolapsing between stent struts into the vessel lumen and extending ≥500 μm in thickness).

Table 1. Patient Characteristics (Patient Basis)

	All Patients, n=507	Patients With DoCE, n=61	Patients Without DoCE, n=446	*P* Value
Age, y*	63 (55–72)	64 (53–75)	63 (55–71)	0.630
BMI*	26 (24–29)	27 (24–30)	26 (24–29)	0.934
Female sex (%)	100 (19.7)	11 (18.0)	89 (20.0)	0.738
Left ventricle ejection fraction (%)*	55 (45–60)	48 (40–58)	55 (47–60)	<0.001
Hypertension (%)	345 (68.0)	43 (70.5)	302 (67.7)	0.658
Hypercholesterolemia (%)	276 (54.4)	31 (50.8)	245 (54.9)	0.679
Smoking habit (%)	203 (40.0)	23 (37.7)	180 (40.4)	0.780
Family history of CAD (%)	159 (31.4)	10 (16.4)	149 (33.4)	0.011
Diabetes mellitus (%)	86 (17.0)	15 (24.6)	71 (15.9)	0.099
CKD, GFR <60 mL min^{-1} 1.73 m^{-2} (%)	80 (15.8)	12 (19.7)	68 (15.2)	0.150
Multivessel disease (%)	256 (50.5)	33 (54.1)	223 (50.0)	0.890
Previous MI (%)	93 (18.3)	19 (31.1)	74 (16.6)	0.008
Previous revascularization (%)				
Previous PCI (%)	92 (18.1)	13 (21.3)	79 (17.7)	0.478
Previous CABG (%)	15 (3.0)	3 (4.9)	12 (2.7)	0.406
Diagnosis				
STEMI (%)	265 (52.3)	28 (45.9)	237 (53.1)	0.339
NSTEMI (%)	85 (16.8)	19 (31.1)	66 (14.8)	0.002
Unstable angina (%)	157 (31.0)	14 (23.0)	143 (32.1)	0.184

BMI indicates body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; DoCE, device-oriented cardiovascular events (including cardiac death, target vessel myocardial infarction, and target vessel revascularization); GFR, glomerular filtration rate; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation MI.

*Expressed as median and quartiles.

lesions in which an MSA <4.5 mm^2 was not associated with an MLA <4.5 mm^2; in these cases, a mean malapposition area percentage of 9.1±4.2% was recorded.

In particular, patients with ST-elevation ACS diagnosis showed more frequently intrastent plaque/thrombus protrusion >500 µm (38.1% versus 26.9%; *P*=0.006), but the amount of prolapse was similar with or without thrombectomy strategy (0.46±0.25 versus 0.45±0.25; *P*=0.796).

DoCE Predictors

During the observed follow-up (median days 345 [quartiles 219–540]), a DoCE occurred in 12.0% of patients, including 2.8% of cardiac mortality, 8.3% of nonfatal target vessel MI, 7.3% of target lesion revascularization, and 4.9% of definite/probable stent thrombosis (Table 4). Notably, 84% of adverse events occurred within the first 12 months after the procedure with a median time to DoCE of 18 days (interquartiles 1–234). No premature dual antiplatelet therapy discontinuation was documented in these cases. Dual antiplatelet therapy regimens included clopidogrel in 50.4%, prasugrel in 33.1%, and ticagrelor in 16.5% of patients with no significant difference among patients with or without adverse events.

When compared with patients without events, patients experiencing DoCE during follow-up showed a higher cardiovascular risk profile characterized by more frequent non-STEMI diagnosis (31.1% versus 14.8%; *P*=0.002) with previous MI (31.1% versus 16.6%; *P*=0.008), lower median left ventricular ejection fraction (48% [quartiles 40–58] versus 55% [quartiles 47–60]; *P*<0.001) and occurrence of coronary artery disease family history (16.4% versus 33.4%; *P*=0.011), and slightly higher prevalence of diabetes mellitus (24.6% versus 15.9%; *P*=0.099; Table 1).

About the procedural aspects, patients with DoCE were characterized by more frequent treatment of ostial (8.5% versus 3.5%; *P*=0.027) or in-stent restenosis lesions (8.5% versus 2.7%; *P*=0.025; Table 2), with smaller stent diameter (3.0 [quartiles 2.5–3.2] versus 3.0 [quartiles 2.75–3.4]; *P*=0.035) and higher bare metal stent use (39.4% versus 25.7%; *P*=0.022).

Among the prespecified OCT criteria, patients with DoCE showed a higher prevalence of in-stent MLA <4.5 mm^2 (42.3% versus 19.3%, HR, 2.72; *P*<0.001), MSA <4.5 mm^2 (31.0% versus 19.7%, HR, 1.87; *P*=0.017), intrastent plaque/thrombus protrusion >500 µm (36.6% versus 31.5%, HR, 2.35; *P*=0.002), dissection width >200 µm at the distal stent edge (18.3% versus 6.4%, HR, 3.84; *P*<0.001), and reference lumen area <4.5 mm^2 in the presence of residual significant plaque at either the distal (25.4% versus 3.7%, HR, 6.07; *P*<0.001) or proximal (14.1% versus 0.8%, HR, 8.50; *P*<0.001) stent edges. Conversely, in-stent MLA <70% of the average reference lumen area (31.0% versus 23.4%, HR, 1.28; *P*=0.335), dissection at the proximal stent edge (9.9% versus 6.6%, HR, 1.44; *P*=0.358), and malapposition >200 µm (49.3% versus

Table 2. Procedural Characteristics (Lesion Basis)

	All Lesions, n=588	Lesions With DoCE, n=71	Lesions Without DoCE, n=517	*P* Value
Treated vessel				
Left main (%)	18 (3.1)	3 (4.2)	15 (2.9)	0.810
Left anterior descending artery (%)	311 (52.9)	41 (57.8)	270 (52.2)	0.455
Left circumflex artery (%)	110 (18.7)	15 (21.1)	95 (18.4)	0.693
Right coronary artery (%)	147 (25.0)	12 (16.9)	135 (26.1)	0.125
Graft conduit (%)	2 (0.3)	0 (0.0)	2 (0.4)	0.574
Lesion features				
Ellis class B2/C (%)	430 (73.1)	47 (66.2)	383 (74.1)	1.000
Calcific lesion (%)	82 (13.9)	11 (15.5)	71 (13.7)	0.707
Ostial lesion (%)	24 (4.1)	6 (8.5)	18 (3.5)	0.027
Bifurcation lesion (%)	63 (10.7)	11 (15.5)	52 (10.1)	0.140
Angiographic ambiguous lesion (%)*	51 (8.7)	8 (11.3)	43 (8.3)	0.343
In-stent restenosis lesion (%)	20 (3.4)	6 (8.5)	14 (2.7)	0.025
Stent thrombosis (%)	22 (3.7)	4 (5.6)	18 (3.5)	0.501
Technical approach				
Direct stenting (%)	161 (27.4)	19 (26.8)	142 (27.5)	1.000
Thrombectomy use (%)	147 (25.0)	15 (21.1)	132 (25.5)	0.556
Postdilation (%)†	282 (48.0)	253 (48.9)	29 (40.8)	0.490
DES (%)	400 (68.0)	42 (59.2)	358 (69.3)	0.116
BMS (%)	161 (27.4)	28 (39.4)	133 (25.7)	0.022
BVS (%)	27 (4.6)	1 (1.4)	26 (5.0)	0.287
Overlapping stent (%)	121 (20.6)	12 (16.9)	109 (21.1)	0.440
Optimal angiographic result (%)	524 (89.1)	62 (87.3)	462 (89.4)	1.000
Stent diameter, mm†	3.0 (2.75–3.5)	3.0 (2.5–3.2)	3.0 (2.75–3.4)	0.035
Stent length, mm†	19 (15–28)	18 (15–24)	20 (16–28)	0.061
Max pressure during stent implantation, atm	16 (14–18)	16 (14–18)	16 (14–18)	0.898
Contrast dye, mL	240 (190–300)	225 (200–300)	240 (190–300)	0.898
Creatinine peak, mg/dL†	0.96 (0.8–1.2)	1.07 (0.9–1.3)	0.96 (0.8–1.1)	0.153

BMS indicates bare metal stent; BVS, bioresorbable vascular scaffold; DES, drug-eluting stent; and DoCE, device-oriented cardiovascular events (including cardiac death, target vessel myocardial infarction, and target vessel revascularization).

*Defined as intermediate lesion with irregular contour and haziness.

†Expressed as median and quartiles.

47.8%, HR, 1.08; *P*=0.734) were not associated with adverse events (Table 3).

OCT analyses revealed a significantly higher prevalence of suboptimal stent deployment parameters (at least 1 OCT finding significantly associated with DoCE) in lesions associated with any adverse event during follow-up (77.5% versus 52.0%; *P*<0.01; Figure 2). In the multivariable Cox hazard analysis, suboptimal OCT stent implantation, defined as the presence of at least 1 OCT finding significantly associated with DoCE, was found to be an independent predictor of worse outcome (HR, 3.69; 95% CI, 1.6–8.4; *P*=0.002) together with impaired left ventricular ejection fraction (HR, 2.17; 95% CI, 1.1–4.4; *P*=0.031), non-STEMI diagnosis (HR, 3.49; 95% CI, 1.8–6.7; *P*<0.001), and in-stent restenosis lesion treatment (HR, 3.97; 95% CI, 1.4–11.4; *P*=0.010). In particular, the presence of a residual intrastent plaque/thrombus protrusion >500 µm was significantly associated with increased DoCE risk (HR, 2.83; 95% CI, 1.3–6.1; *P*=0.008) with a more evident negative impact in patients presenting with ST-elevation (HR, 4.09; 95% CI, 1.1–15.2; *P*=0.035) than in patients without ST-elevation (HR, 2.82; 95% CI, 1.1–7.5; *P*=0.039). This more evident impact is mainly because of the fact that these patients are at substantially at higher risk, but not because of an epidemiologically or nominally statistical significance of their product (ie, statistical interaction). Figures 3 and 4 have summarized the impact of an OCT-defined suboptimal stent implantation

Table 3. OCT Findings (Lesion Basis)

	All Lesions, n=588	Lesion With DoCE, n=71	Lesion Without DoCE, n=517	*P* Value
OCT features				
In-stent MLA, mm^2	6.1±2.2	5.4±2.0	6.2±2.2	0.007
Maximum in-stent lumen diameter, mm	3.0±0.6	2.9±0.5	3.1±0.6	0.014
Minimum in-stent lumen diameter, mm	2.4±0.5	2.3±0.5	2.5±0.5	0.023
Lumen symmetry (%)	1.3±0.2	1.3±0.2	1.3±0.2	0.546
Stent expansion (%)*	84.9±22.4	82.1±23.1	85.3±22.3	0.268
Minimum stent area, mm^2	6.3±2.3	5.6±1.8	6.4±2.3	0.007
Atherothrombotic tissue at MLA, mm^2	0.5±0.6	0.4±0.5	0.5±0.6	0.548
Atherothrombotic tissue at MLA (%)	6.7±9.3	7.7±10.8	6.6±9.1	0.848
Mean reference lumen area, mm^2	7.3±2.7	6.5±2.6	7.4±2.8	0.008
Distal reference lumen area, mm^2	6.5±2.9	5.6±2.4	6.6±2.9	0.008
Proximal reference lumen area, mm^2	8.2±3.4	7.3±3.0	8.4±3.4	0.013
Malapposition thickness, mm	0.23±0.2	0.2±0.2	0.2±0.2	0.658
Malapposition length, mm	2.9±3.5	2.4±2.5	3.0±3.6	0.197
Intrastent atherothrombotic tissue prolapse, mm	0.42±0.3	0.5±0.3	0.4±0.3	0.019
Distal edge dissection length, mm	0.25±1.1	0.76±2.5	0.18±0.6	<0.001
Distal edge dissection width, mm	0.04±0.1	0.12±0.2	0.03±0.1	<0.001
Distal edge dissection arc (°)	8.0±29.3	26.0±60.8	5.5±20.6	<0.001
Proximal edge dissection length, mm	0.16±0.6	0.30±1.1	0.13±0.5	0.044
Proximal edge dissection width, mm	0.04±0.1	0.05±0.1	0.03±0.1	0.304
Proximal edge dissection arc (°)	5.6±18.3	9.9±24.9	5.0±17.1	0.040
Suboptimal OCT criteria				
In-stent MLA <4.5 mm^2 (%)	130 (22.1)	30 (42.3)	100 (19.3)	<0.001
MSA <4.5 mm^2 (%)	124 (21.1)	22 (31.0)	102 (19.7)	0.028
Residual stenosis (%)†	143 (24.3)	22 (31.0)	121 (23.4)	0.187
Malapposition >200 μm (%)	282 (48.0)	35 (49.3)	247 (47.8)	0.899
Intrastent atherothrombotic tissue prolapse >500 μm (%)	189 (32.1)	26 (36.6)	163 (31.5)	0.009
Edge dissection >200 μm (%)	79 (13.4)	16 (22.5)	63 (12.2)	0.026
Distal dissection (%)	46 (7.8)	13 (18.3)	33 (6.4)	0.001
Proximal dissection (%)	41 (7.0)	7 (9.9)	34 (6.6)	0.464
Reference narrowing (%)‡	45 (7.7)	24 (33.8)	21 (4.1)	<0.001
Distal narrowing (%)	37 (6.3)	18 (25.4)	19 (3.7)	<0.001
Proximal narrowing (%)	14 (2.4)	10 (14.1)	4 (0.8)	<0.001

DoCE indicates device-oriented cardiovascular events (including cardiac death, target vessel myocardial infarction, and target vessel revascularization); MLA, minimum lumen area; MSA, minimum stent area; and OCT, optical coherence tomography.

*Defined as stent-to-mean reference lumen area.

†Defined as in-stent minimum lumen area <70% of the average reference lumen area.

‡Defined as reference lumen area <4.5 mm^2 in the presence of significant residual plaque adjacent to stent endings.

and the individual effect of residual intrastent plaque/thrombus protrusion on outcome among all the prespecified OCT predictive parameters (see also Data Supplement Tables I and II).

Discussion

The main findings of this study are the following: (1) OCT assessment of culprit treated lesion in ACS patients undergoing urgent/emergent PCI allowed the identification of quantitative morphological findings independently associated with outcome (HR, 3.69; 95% CI, 1.6–8.4; *P*=0.002), and (2) in the acute setting significant residual culprit lesion intrastent plaque/thrombus protrusion is observed in one third of cases and is significantly associated with DoCE occurrence (HR, 2.83; 95% CI, 1.3–6.1; *P*=0.008).

Table 4. Clinical Outcomes (Patient Basis)

	All Patients, 507	Patients With OCT Suboptimal Stent Deployment*, 280	Patients Without OCT Suboptimal Stent Deployment, 227	HR (CI)	*P* Value
DoCE (%)	61 (12.0)	50 (17.9)	11 (4.8)	4.12 (2.1–7.9)	<0.001
Cardiac death (%)	14 (2.8)	12 (4.3)	2 (0.9)	5.42 (1.2–24.4)	0.028
Myocardial infarction (%)	42 (8.3)	33 (11.8)	9 (4.0)	3.27 (1.6–6.9)	0.002
Periprocedural	12 (2.4)	8 (2.9)	4 (1.8)	1.69 (0.5–5.6)	0.671
During follow-up	30 (5.9)	25 (8.9)	5 (2.2)	4.57 (1.7–12.0)	0.002
Target lesion revascularization (%)	37 (7.3)	31 (11.1)	6 (2.6)	4.76 (2.0–11.4)	<0.001
Stent thrombosis (%)	25 (4.9)	21 (7.5)	4 (1.8)	4.65 (1.6–13.6)	0.005
Acute	5 (1.0)	3 (1.1)	2 (0.8)	1.29 (0.2–7.7)	0.782
Subacute	16 (3.1)	14 (5.0)	1 (0.4)	11.81 (1.6–89.8)	0.017
Late	2 (0.4)	3 (1.1)	0 (0.0)	0.00 (0.0–0.0)	0.257
Very late	2 (0.4)	1 (0.3)	1 (0.4)	1.33 (0.8–22.5)	0.843
Days of follow-up†	345 (219–540)	342 (205–540)	352 (230–540)		0.202

CI indicates confidence interval; DoCE, hierarchical device-oriented cardiovascular events (cardiac death, target vessel myocardial infarction, and target lesion revascularization); HR, hazard ratio; and OCT, optical coherence tomography.

*Either in-stent minimum lumen area <4.5 mm^2, intrastent atherothrombotic tissue prolapse >500 µm, dissection >200 µm at the distal stent edge, distal or proximal reference narrowing.

†Expressed as median and quartiles.

The OCT imaging technique with its high axial resolution has represented a new promising angle of view to address the adequacy of stent deployment and its enduring interaction with plaque/vessel components.[3,27,28] Recent studies demonstrated the possibility to identify end-procedural stent parameters having negative consequence on clinical outcome and suggested the usefulness of an OCT-guided PCI strategy.[6,7,12,23] The CLI-OPCI I study, comparing angiography alone versus angiographic plus OCT guidance for routine PCI, firstly supported the clinical use of OCT guidance and raised the question of proper management of observed OCT findings.[6] An observational OCT study in patients undergoing fractional flow reserve and PCI (ILUMIEN I [Observational Study of Optical Coherence Tomography in Patients Undergoing Fractional Flow Reserve and Percutaneous Coronary Intervention]) showed how OCT findings influenced physician decision-making especially in more complex coronary lesions; in particular, malapposition, edge dissection, and stent underexpansion that are not apparent on angiography were the main reasons driving additional reaction by operators.[29] The Massachusetts General Hospital OCT Registry showed 900 stable and unstable lesions, a frequent incidence of abnormal post-stent OCT findings, identifying irregular intrastent protrusion

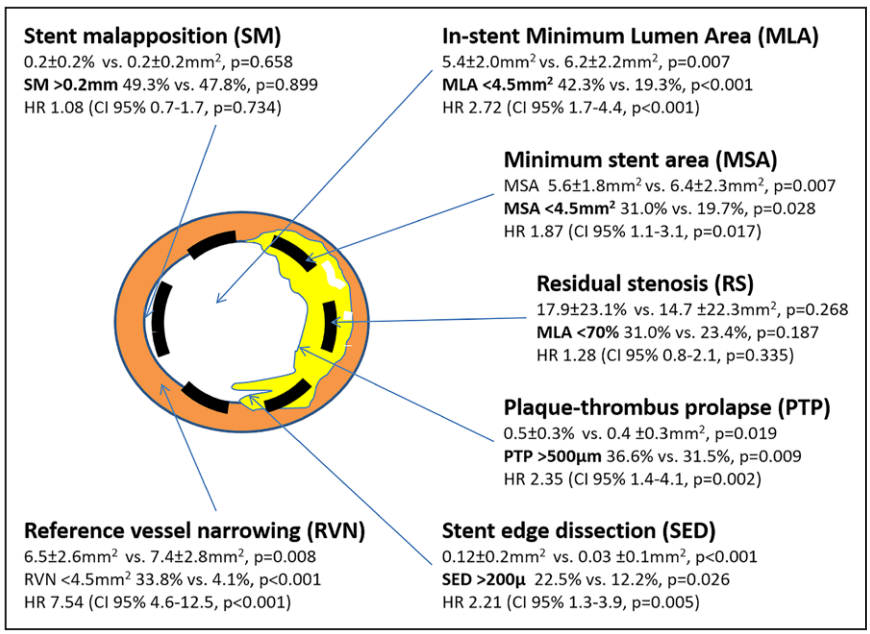

Figure 2. Optical coherence tomographic (OCT) criteria applied to address suboptimal OCT stent deployment with relative incidence in patient without and with any adverse event during follow-up. CI indicates confidence interval; and HR, hazard ratio.

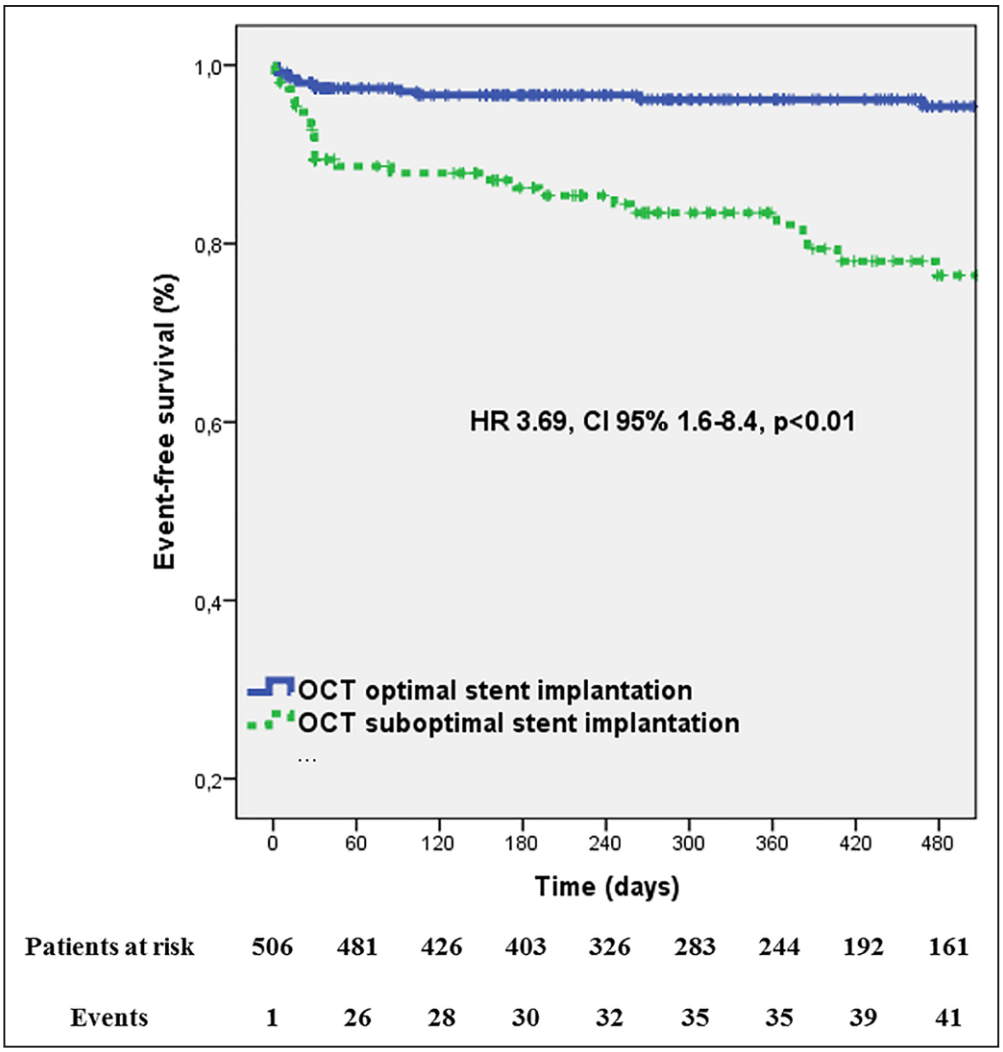

Figure 3. Survival free of device-oriented cardiovascular events according to optimal vs nonoptimal stent deployment assessed using optical coherence tomographic (OCT) predictive parameters. CI indicates confidence interval; and HR, hazard ratio.

and small MSA as important predictors of adverse events, primarily target lesion revascularization.[12] Finally, the CLI-OPCI II study, including ≈1000 lesions, helped to better define the quantitative threshold of suboptimal OCT stent implantation parameters[7]: in-stent MLA <4.5 mm^2, dissection >200 µm at the distal stent edge, and reference lumen area <4.5 mm^2 in the presence of residual significant plaque at stent edges resulted as independent predictors of worse outcome at follow-up.

Use of OCT Parameters in an Unstable Setting

On the basis of the previous evidences, in this study, we sought to evaluate the clinical impact of suboptimal OCT stent implantation in an unexplored clinical environment: culprit lesion(s) of ACS patients. We addressed the predictive accuracy of all the quantitative OCT parameters identified in the CLI-OPCI II study in this specific population. In particular, we focused our attention on the residual intrastent plaque/thrombus protrusion, which is an indistinct mesh of thrombus, lipid necrotic core debris protrusion, and fragmented plaque.

According to the prespecified OCT definitions, at least 1 criterion of clinically relevant suboptimal stent implantation was found in about half of patients and was associated with an associated increased risk of DoCE during follow-up (17.9% versus 4.8%; HR, 4.12; 95% CI, 2.1–7.9; *P*<0.001). When compared with the CLI-OCPI II study population that also included elective patients with stable coronary artery disease, prevalence of the OCT-defined suboptimal stent deployment was significantly higher in ACS patients (55.2% versus 31.0%; *P*<0.01), confirming that acute patients were at increased risk of suboptimal PCI results.

Lesions associated with DoCE during follow-up revealed a significantly higher prevalence of suboptimal OCT-detected stenting parameters. In particular, in-stent MLA <4.5 mm^2, MSA <4.5 mm^2, intrastent atherothrombotic tissue prolapse >500 µm, dissection width >200 µm at the distal stent edge, and reference lumen area <4.5 mm^2 in the presence of residual significant plaque at stent edges were significantly more frequent in cases of DoCE occurrence during follow-up.

Notably, in the acute setting, stent malapposition (>200 µm) was not associated to a worse outcome; indeed, DoCE rate was very similar in patients with or without OCT-detected acute stent malapposition (12.8% versus 11.4%; *P*=0.730). This result confirmed the previous intravascular ultrasound

and OCT findings that failed to relate acute stent–vessel wall malapposition with clinical outcome.[12,30–32] Similarly, the presence of residual stenosis (in-stent MLA >30% of the average reference lumen area) failed to predict outcome confirming that, also in acute setting, the absolute in-stent MLA and MSA are more predictive than stenosis expressed as percentage of stent-to-mean reference lumen area.[5,33–36]

The Role of Residual Intrastent Plaque/Thrombus Protrusion

The presence of residual plaque/thrombus prolapse was a common finding, detectable in most of the culprit lesions of STEMI patients regardless of the adopted PCI strategy.[11,37] Previous angiographic studies related intrastent residual thrombus to an increased risk of periprocedural MI (ie, distal embolization) and stent thrombosis (eg, inadequate vessel healing).[8–10] In intravascular ultrasound studies, the intrastent tissue prolapse has been associated with a worse prognosis in the setting of PCI for acute MI.[38–40] These findings were partially corroborated by preliminary OCT data that were able to relate residual intrastent plaque/thrombus prolapse to surrogate clinical end points such as coronary flow, myocardial reperfusion,[37] and neointimal volume.[41] The Massachusetts General Hospital OCT Registry demonstrated a correlation between intrastent plaque protrusion (>100 μm in 53% of lesions) and the following risk or target lesion revascularization in the first year of follow-up; thrombus prolapse (defined as a mass with diameter >250 μm attached to the luminal surface, stent strut, or floating within the lumen) was observed in 39% of lesions but was not predictive of worse outcome.[12] The choice of arbitrary cut-offs, the qualitative interpretation of plaque protrusion, and the coexistence of stable and acute patients might partially explain these results.

Thus, because of the lack of solid end points and specific studies, the true clinical impact of residual intrastent plaque/thrombus protrusion in acute patients remained undefined. In the CLI-OCPI II study,[7] we explored the clinical role of intrastent atherothrombotic tissue prolapse (applying a 500 μm thickness cut-off) in a mixed population which included both acute and stable patients; in this study, intrastent plaque/thrombus protrusion was not an independent predictor of outcome (HR, 1.21; 95% CI, 0.7–1.9; P=0.45). On the other hand, in this study, we proved a correlation between residual intrastent plaque/thrombus protrusion and clinical outcome for patients with ACS. In fact, at the multivariable Cox hazard analysis, residual intrastent plaque/thrombus protrusion >500 μm was a 3-fold independent DoCE predictor (HR, 2.83; 95% CI, 1.3–6.1; P=0.008; Figure 4). The explanation for the discrepancy between this substudy and the overall CLI-OPCI II registry likely reflected the differences in tissue composition (ie, thrombus or plaque fragments) because the prevalence of intrastent tissue prolapse was similar (32.1% versus 29.4%). The higher intrastent thrombotic burden could also explain the significant rate of subacute stent thrombosis (5%) observed in this study.

Unfortunately, OCT, despite its high definition, has been unable to distinguish thrombus from the fragmented plaque protruding within the stent struts. For this reason, we applied the comprehensive term plaque/thrombus to describe tissue prolapse. However, it was very likely that the residual intrastent tissue observed in an unstable setting was mainly made of thrombus or lipid necrotic debris components, although a predominance of atheroma components, including fibrous tissue, was more common in stented culprit lesions of stable patients.

Interplay Among OCT Features of Stent Positioning in Patients With ACS

In this study, we evaluated many parameters: intrastent plaque/thrombus protrusion and in-stent MLA and MSA, with the latter being assessed in all cases at the MLA site plus at different sites if the stent area at MLA site was not the smallest. This comprehensive assessment provided information on the clinical interplay among OCT metrics of stent positioning. Notably, in most cases, MLA and MSA were located in the same OCT frame; in 18.5% of lesions, MLA was <4.5 mm^2 notwithstanding a well-expanded stent (MSA >4.5 mm^2) primarily because of intrastent plaque/thrombus protrusion. However, in-stent MLA <4.5 mm^2 showed the strongest correlation with DoCE compared with MSA <4.5 mm^2 (HR, 2.72 versus HR, 1.87, respectively). Thus, in ACS patients, the high prevalence of intrastent lipid-rich debris and thrombus components negatively impacted on final in-stent lumen dimension, but not on the MSA itself.

Removal of intrastent thrombus remains an open issue for interventional cardiologists. Recent data from the COCTAIL II[37] and TROFI[42] trials showed no difference in terms of residual intrastent atherothrombotic area regardless of the prestent thrombotic load and the different strategies adopted in primary PCI, including thrombus aspiration or local drug delivery of abciximab. Thus, these data seem to suggest that also in acute patients, a more aggressive protocol should be applied by interventional cardiologists to reduce intrastent tissue prolapse or its distal embolization, potentially including prolonged higher pressure balloon inflations,[42] distal protection, or even mesh stents together with pharmaceutical solutions such as more potent antiplatelet agents.

Limitations

The nonrandomized, retrospective design represented the main limitation of this study, including patients uniquely pooled by the arbitrary intraprocedural OCT use. Thus, these patients represented a selected PCI subgroup not necessarily representative of general population. This could partially explain the unusual rate of subacute ST stent thrombosis observed, perhaps limiting the external validity of these results. Notwithstanding evident clinical (ie, baseline risk profile), procedural (ie, bare metal stent versus drug-eluting stents use), and medical (eg, dual antiplatelet therapy protocol) differences among patients, the presence of nonoptimal OCT criteria for stent deployment was confirmed as an independent predictor of DoCE in the multivariable Cox hazard analysis. The absence of data on baseline OCT assessment of the lesions and the effective intraprocedural OCT use by operators, as well as the lack of angiographic/OCT follow-up, represented other study limitations. Third, OCT could not reliably differentiate thrombus and plaque intrastent protrusion; it is likely that these 2 components play a different role in the plaque/vessel healing. Indeed, although the incidence of tissue protrusion in acute patients is relatively frequent, it spontaneously resolves in most of cases suggesting a predominance of thrombotic material.[43] On the

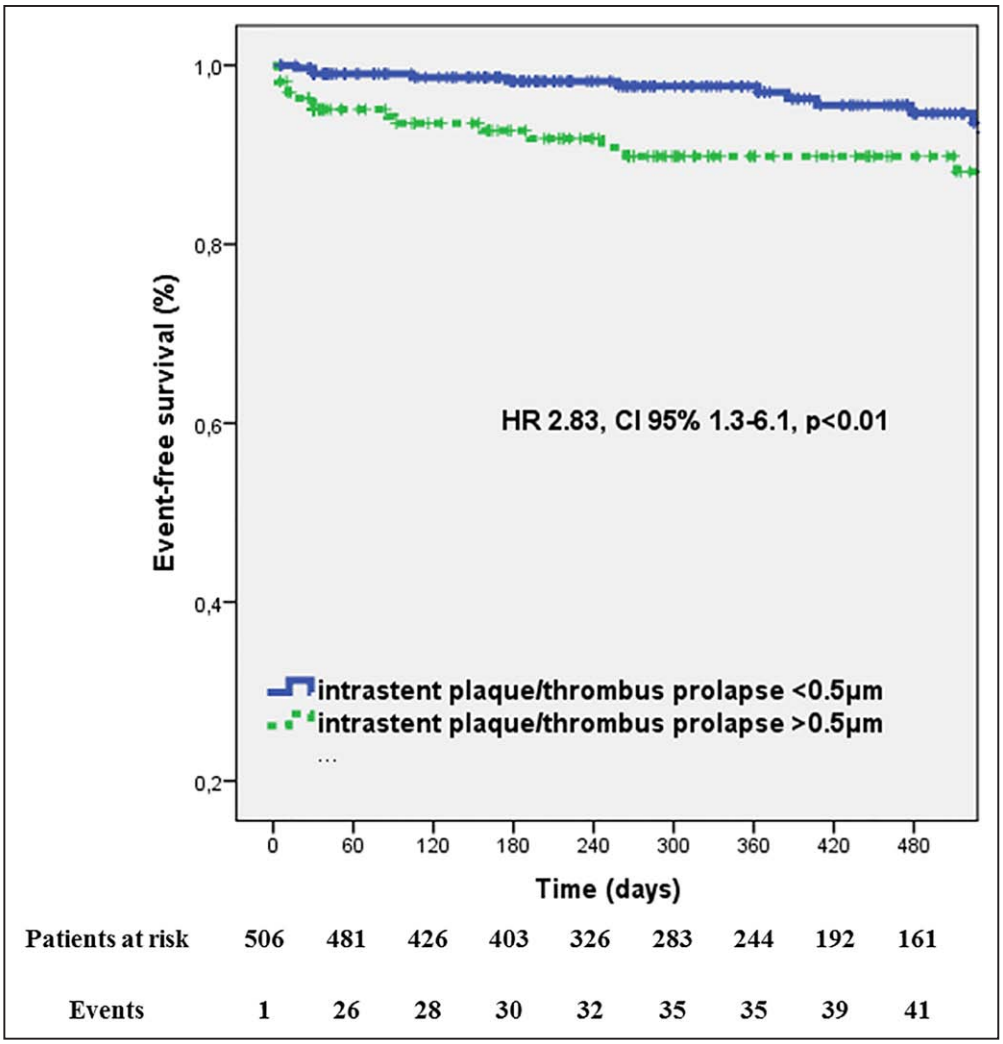

Figure 4. Impact on event free-survival of residual vs no residual intrastent plaque/thrombus protrusion >500 µm. CI indicates confidence interval; and HR, hazard ratio.

other hand, the presence of a persistent atheroma protrusion could negatively affect the neointimal hyperplasia formation.[44] Long-term OCT assessment is required to further investigate the evolution and the clinical impact of plaque/thrombus intrastent protrusion in acute setting.

Conclusions

In ACS patients, the presence of OCT-defined suboptimal stent deployment was an independent adverse clinical outcome predictor. Unlike previous findings in the stable setting, significant residual intrastent plaque/thrombus protrusion after PCI was associated with an increased risk of DoCE recurrence at follow-up in ACS patients.

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Disclosures

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