Stent Thrombosis

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Abstract

The occurrence of stent thrombosis (ST) is rare but it remains one of the most dreadful complications following Percutaneous Coronary Intervention (PCI), due to the possible risk of death and extensive myocardial infarction. OCT contributes critically in the assessment of ST with substantial clinical implications through: (1) a better mechanistic understanding of the different processes involved; (2) the identification of surrogate markers anticipating the risk of ST; (3) a tailored and more effective approach for the acute treatment of ST. The high level of accuracy in the measurements and separation of the plaque and thrombus components along the entire vessel, and in the fine details on tissue coverage at the stent strut level, makes OCT a unique intracoronary imaging modality for assessing stent failures and guiding appropriate interventions during ST.

Keywords

Optical coherence tomography • Stent thrombosis • Myocardial infarction • Inadequate stent implantation • Stent malapposition • Uncovered struts • Neoatherosclerosis

11.1 Introduction

The increased burden of coronary artery disease (CAD) represents a major challenge to the global health care system. Over the last decades the number of patients undergoing percutaneous coronary interventions (PCI) substantially increased, with more complex clinical and anatomical settings treated with stent implantation. Acute myocardial infarction, unprotected left main disease and complex bifurcation are regularly treated with coronary stents. This approach was made possible by the development and widespread use of drug-eluting stents (DES) that effectively reduced the limit of in-stent restenosis following bare metal stent implantation [1, 2]. Nevertheless, the extensive use of DES in high risk cohorts was plagued by an increasing number of stent thrombosis (ST), especially in the late and very late phases after the DES implantation, associated with a high rate of mortality [3–5].

11.2 Definition and Incidence

The definition of ST varies from an "angiographically proven" to a "clinically suspected" event with the inclusion of acute myocardial infarction (MI) involving the target vessel, and unexplained death (within 30 days or anytime). The Academic Research Consortium (ARC) divided ST according to the level of certainty in source documentation and frequency of occurrence compared to the index procedure [6]. Definite ST (highest level of certainty) requires either angiographic or postmortem evidence of thrombotic stent occlusion that has to be in the stent or in the 5 mm segment immediately apart from the stent. Conversely, probable ST

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encompasses any unexplained death within 30 days of stent implantation or any MI in the territory of the implanted stent, regardless of the time span. Finally, possible ST includes any unexplained death beyond 30 days. All these entities are subdivided temporally into acute (<24 h), sub-acute (1–30 days), late (between 30 days and 1 year) and very late ST (>1 year after stent implantation).

ST limited during the early phase of bare-metal-stent (BMS) the rate of ST was as high as 20 % [7]. Following the introduction of high pressure balloon post- dilatation and the combined use of dual antiplatelet therapy (DAPT), a significant decrease of ST was observed [8–14], with a range between 0.5 and 4 %. In the Dutch registry that included more than 21,000 patients treated with BMS and first generation DES, the vast majority of ST (>70.0 %) occurred in the first month after stent implantation, with a cumulative rate of 2.1 % in definite ST over a 3-years follow-up period [15]. A similar occurrence of ST was observed in the Bern-Rotterdam registry, that followed 8,146 patients treated with first generation DES (paclitaxel eluting stent [PES] and sirolimus eluting stent [SES]), with 3.3 % of cumulative incidence of ST at 3-years [16]. Furthermore, the specific concern for additional risk of very late ST observed in the first generation DES at an annual rate of 0.5 % [16–18] was addressed by these studies. More recently, following the widespread adoption of current generation DES, with thinner struts and a more biocompatible polymer, a substantial reduction of ST has been reported [19, 20].

11.3 Clinical Outcomes

Very few studies have been published on the long-term clinical outcomes following a first episode of definite ST. Some series reported a mortality rate associated with ST of up to 45 % [13, 21–23]. Interestingly, the observed rate of recurrent episodes of ST was approximately 20 %. In a recent meta-analysis of 23 studies that evaluated 7,315 cases of definite ST, this event was associated with an in hospital mortality of 8 % and an in–hospital new or recurrent MI rate of 6 % (not counting for the ST event). Notably, the stent type had no significant effect on in-hospital or 30-day mortality [24].

11.4 Associated Factors

Several studies have confirmed the multifactorial nature of ST. ST may depend on: (1) patient characteristics and risk factors, (2) treated lesion and procedural-related factors, including the stent type and (3) DAPT compliance and responsiveness [13, 21–33]. Patients clinical characteristics associated with ST include diabetes mellitus, acute coronary syndromes (in particular ST-elevation myocardial infarction [STEMI]) as indication for PCI, left ventricular dysfunction, renal failure, younger age, smoking status, malignancy and presence of bleeding. Moreover some angiographic characteristics of the stented lesion, including small vessel diameter, bifurcations, heavy calcified lesions, ostial and long lesions have been associated with increased risk of ST. In addition, procedural characteristics (multiple stents implantation, stent undersizing and under expansion, total stent length, balloon/stent size ratio, bivalirudin administration, and stent type) may also predict the individual risk to develop ST. Among the technical aspects more critically involved in early ST the presence of residual dissection and stent underexpansion seem to play major roles. Finally, individual DAPT responsiveness may substantially contribute to ST occurrence. Indeed, both BMS and DES implantation induce platelet adhesion, activation and thrombus formation [32, 33]. Therefore, effective anti-platelet therapy is strongly recommended during and after stent implantation. The awareness of the potential for late and very late ST has prompted a shift towards prolonged (12 months or more) duration of DAPT, which is in turn is associated with increased bleeding risk, entails increased costs and interferes with invasive and surgical procedures, if required.

11.5 The Pathology View

Different pathological mechanisms are associated with ST. The information on coronary vessel response after stent implantation was essentially derived from two sources – translational preclinical models and human autopsy series. Different factors are involved in the pathogenesis of early and late ST. Nakano et al. recently reported the histopathology features of early ST in 34 patients presenting with Acute Coronary Syndrome (ACS), who underwent an implant with BMS, first or second generation DES. Interestingly, the authors found that the underlying plaque morphology (prolapse of the necrotic core), the thrombus burden, medial tear and incomplete apposition were more frequently observed at the level of cross-sections containing thrombus compared with patent cross-sections in the same stent [34]. These findings support the concept that plaque morphology as well as procedural and mechanical-related factors play a role in acute/subacute ST. These pathological findings are also in line with the results of the previous angiographic and intravascular ultrasound (IVUS) studies which demonstrated that the presence of residual edge dissection and significant remaining stenosis in proximal and/or distal reference segments can significantly increase the risk of early ST [31].

Histopathology has also demonstrated delayed healing and incomplete endothelial stent coverage as the most

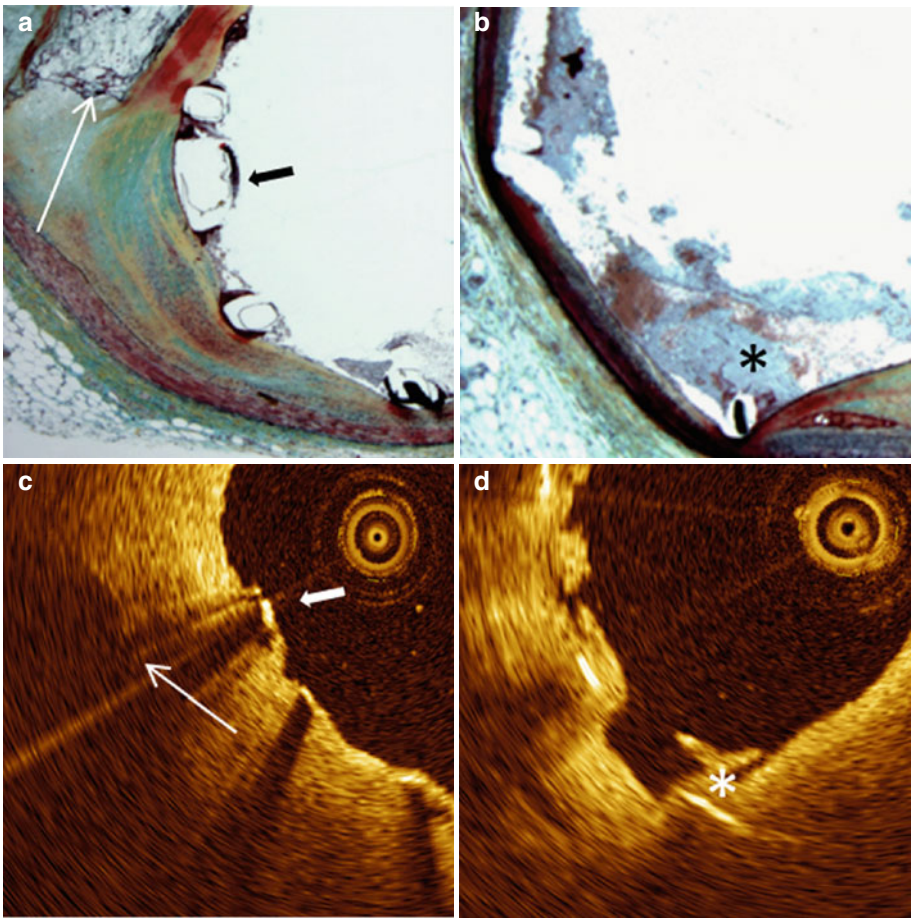


Fig. 11.1 Histology and OCT. (**a**) and (**b**) Magnified histology sections (Movat pentachrome stain) and corresponding OCT image (**c**, **d**) of a specimen of stented coronary artery with implant duration of 48 h. (**a**) Uncovered struts at 9 o'clock (*arrowhead*) and calcium deposition (*arrow*); (**c**) corresponding OCT image. (**b**) Thrombus deposition (*) on top of the uncovered strut at 6 o'clock and (**d**) corresponding OCT image

important factors for late ST after DES implantation [35, 36], (Fig. 11.1). These studies suggested hypersensitivity, with chronic inflammation and late acquired stent malapposition, as possible contributing factors [35–38]. In an *ex-vivo* study comparing DES vs. BMS cases of ST at different time points, endothelialization was nearly complete in BMS examined beyond 6 months, whereas incomplete endothelialization persisted in DES beyond 40 months [34]. More recently neoatherosclerosis, characterized as clusters of lipid-laden foamy macrophages within the neointima, with or without necrotic core [39], has been identified as a frequent cause of late stent failure, including ST. Moreover, pathological reports have demonstrated that neoatherosclerosis is more common and occurs earlier with DES as compared to BMS [40].

11.6 The Role of Intravascular Imaging to Assess Stent Thrombosis

Intracoronary imaging techniques have been developed to provide complementary, more accurate measurements and details to coronary angiography in patients undergoing complex PCI. Compared with IVUS, OCT is superior in the assessment of unstable plaque features, including the presence of thrombus, rupture plaques, thin-cap fibroatheroma (TCFA) and pools of superficial macrophages [41, 42]. In addition, OCT provides superior details on the immediate results of stent implantation (vessel injury, tissue prolapse, stent malapposition and stent geometry distortion). Finally, OCT at the follow-up time is more accurate in assessing the remaining thrombus and the amount and type of tissue growing into the stent, discriminating between covered and uncovered struts, neointimal formation and newly developing atherosclerosis [42–44]. Based on these unique characteristics OCT can critically contribute to a better mechanistic understanding of the pathophysiology of ST and to the identification of surrogate markers, anticipating the risk.

11.7 OCT in Stent Thrombosis: Not All Stent Thrombosis Are Created Equal

The multi-factorial nature of ST and the high risk related to this event favors a fully informative, accurate assessment of the culprit lesion and vessel at time of acute presentation, through high resolution intravascular imaging modalities. Similarly to any acute MI, ST requires immediate thrombus removal and quick restoration of an

effective TIMI flow as the goals of primary interventions. After vessel recanalization, OCT may be used for guiding a more effective thrombus removal, via mechanical and/or additional pharmacological treatments. Further, OCT may help to recognize the stent-related factors (if any) responsible for ST (malapposition, under expansion, incomplete coverage, lipid laden neointima) and to select, based upon the imaging details, the most effective treatment to avoid recurrences. Indeed, while stent under-sizing, under-expansion and other suboptimal PCI results are usually observed in the acute/subacute ST cases, the main mechanisms involved in both late/very late ST are usually linked to the presence of uncovered stent struts and/or neoatherosclerosis.

11.8 How to Perform OCT in the Acute Setting of Stent Thrombosis

The planning for imaging in a patient arriving at the hospital with possible ST should start before the patient's arrival at the Cath Lab. If the patient was treated with stent(s) in the same hospital all clinical and procedural information (comorbidities, clinical presentation at the index procedure, stent type and size, eventually complications at the stent implant) has to be made available to the operator before primary PCI. In patients arriving with ST and TIMI 0–1 flow grade or large filling defect, thrombus aspiration is at the frontline of treatment for reestablishing the flow and allowing subsequent histopathology analysis of the aspirated thrombotic material. In this case thrombus aspiration has to be performed until coronary flow is reestablished and in any case before the OCT imaging pullback. It is relevant to the safety of the patient and equally relevant for having high quality OCT imaging, not to proceed with the OCT scan when the vessel is occluded with no distal flow or in the presence of an extremely high thrombus burden anticipated at the angiography views. Major arrhythmias and images unreadable due to the excess of remaining thrombus are the main reasons for adopting a dedicated strategy. In the presence of a large remaining thrombus the imaging catheter can be occlusive. One possible trick to anticipating if an OCT pullback can be performed with enough quality is a quick check in angiography with a few cc of contrast, maintaining the aspiration catheter at the culprit site. If the contrast passes freely the probability that it will not be occlusive with the image catheter is high and you may proceed with the OCT pullback. A combined use of IVUS and OCT when possible is recommended, since both imaging techniques may provide complementary data on mechanisms of ST. In these cases it seems wise to start with IVUS, since no contrast flushing and no selective coronary intubation is required. IVUS may add unique information on vessel remodeling that cannot be provided by OCT. It is important to remember that OCT imaging may increase the overall amount of procedural contrast. In the presence of hemodynamic instability, frequently observed during ST, the total amount of contrast needs to be strictly monitored. When flow is reestablished the operator should take time to analyze the imaging data, understand the main causative mechanism and the possible contributing factors and to tailor the treatment strategy. Since the time interval between the baseline assessment and the final post-intervention pullbacks can be wide, the OCT catheter should be maintained wet in saline solution to avoid fibrin deposition on the imaging element and contrast medium crystallization.

11.9 Information Provided by OCT

11.9.1 Thrombus Assessment

OCT is able to assess the presence and type of thrombus and the effectiveness of coronary thrombus removal through mechanical and or pharmacological interventions. With OCT, intracoronary thrombus is identified as any abnormal mass protruding into the lumen, with a sharp gap in the underlying tissue, signal backscattering and various degrees of attenuation. White thrombus is characterized by homogeneous signal rich with low-backscattering attenuation, while red thrombus, that contains red blood cells and a network of fibrin, is defined by a highly backscattering and highly attenuated light signal (resembling blood). The presence of a large amount of residual thrombus may preclude a reliable assessment of strut coverage (Fig. 11.2). In these cases additional potent pharmacologic agents, such as GP IIb/IIIa receptor blockers, can be used to allow an accurate assessment of the underlying stent, and to detect possible segmental malapposition or consecutive frames with largely uncovered struts (Fig. 11.3).

11.9.2 Inadequate Stent Implantation

Inadequate stent implantation can be due to a mismatch between lumen dimensions and the selected stent size, or be the consequence of stent under expansion in spite of an adequate stent/artery ratio. Providing automatic lumen profile measurements, novel OCT systems allow for the online detection of inadequate stent implantation.

In a small-scale OCT study evaluating patients with subacute ST [45], a smaller minimal stent area was observed in these patients compared to the uneventful controls, with minimum stent area preferentially located at the thrombus site, indicating stent under expansion as a possible mechanism of

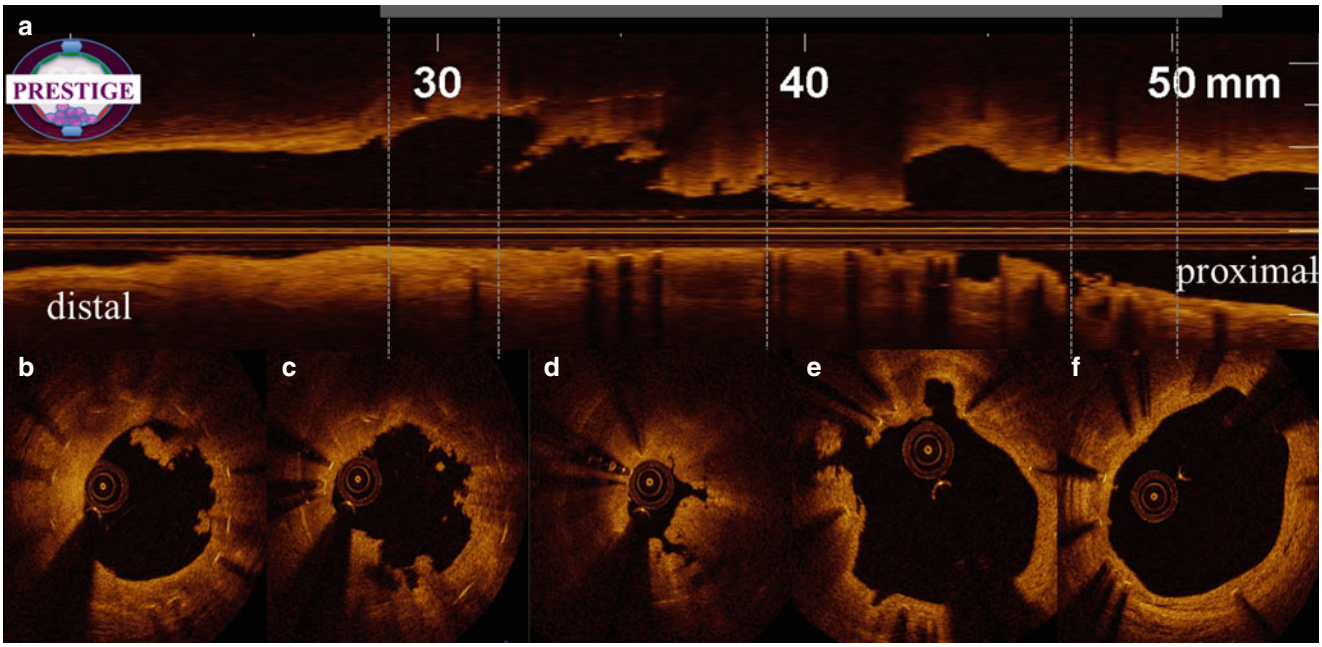


Fig. 11.2 Large amount of residual thrombus after manual thrombus aspiration. OCT longitudinal view (**a**) and multiple cross-sections (**b**–**f**) images during a ST case after thrombus aspiration. Large residual thrombus remained inside the stent (**b**, **c**, **d**). Struts are clearly visible due to shadowing. Proximal (**f**) and distal (**b**) sections indicate complete strut coverage. White thrombus mainly in (**b**, **c**), mixed thrombus in (**d**)

early ST. In addition, the percentage of both uncovered and malapposed struts was significantly higher at the thrombus site compared with their respective control patients.

Illustrative Case 1

Stent Under-Expansion as Primary Cause of Late Stent Thrombosis

A 60 years-old patient underwent a complex PCI procedure on a highly calcified right coronary artery (RCA), requiring rotational atherectomy (Fig. 11.4). Five years later the patient was admitted with diagnosis of inferior STEMI. Coronary angiography revealed an in stent thrombotic occlusion of the RCA. After wire crossing and thrombus aspiration, OCT and IVUS pullbacks were performed. IVUS showed a large amount of residual thrombus and severe stent under expansion at the culprit segment. OCT pullback confirmed stent under expansion in the absence of any uncovered/malapposed struts or abnormal neointima (Fig. 11.5). Severe under expansion was treated with larger balloons and a short EES implanted at high pressure. Final intracoronary imaging confirmed an adequate acute gain in the previously unexpanded stent segment (Fig. 11.6).

11.9.3 Incomplete Stent Apposition

There is increasing interest in the role of incomplete stent apposition (ISA) as a causative factor of ST. ISA is normally defined as the separation of one or more stent struts from the arterial wall, with evidence of blood speckles behind the strut, in the absence of any side branch. According to the time of occurrence, ISA is labeled as acute (post-procedure), persistent (diagnosed at post-procedure and still present at follow-up), and acquired (not present at post-procedure but identified at follow-up). In the absence of any intravascular imaging assessment at the index procedure, ISA is usually classified as late incomplete stent apposition. The role of stent malapposition in the pathogenesis of late ST has been continuously debated advocated as a possible causative factor in some studies and neglected in others. Cook et al. reported an increased incidence of stent malapposition and positive vessel remodeling in patients presenting with very late ST after first generation DES, compared with uneventful controls [46]. ISA was detected in 77 % of patients with very late ST with a wide area of malapposition. Similarly, in a study conducted by Guagliumi and coll. on consecutive cases of late and very late ST assessed with OCT, stent malapposition was observed in 78 % of the all cases, with maximal area of malapposition significantly greater compared to the uneventful matched controls [43]. Recently, the "Mechanism Of Stent Thrombosis" MOST study also demonstrated a three times higher rate of malapposed struts in patients with late ST as compared to controls [45]. Late acquired ISA may essentially be due to two different mechanisms: (a) positive vessel remodeling, as a marker of vessel toxicity in response to the drug and or to the polymer; (b) resolution or reabsorption of a pre-existing soft plaque or thrombus behind the stent struts.

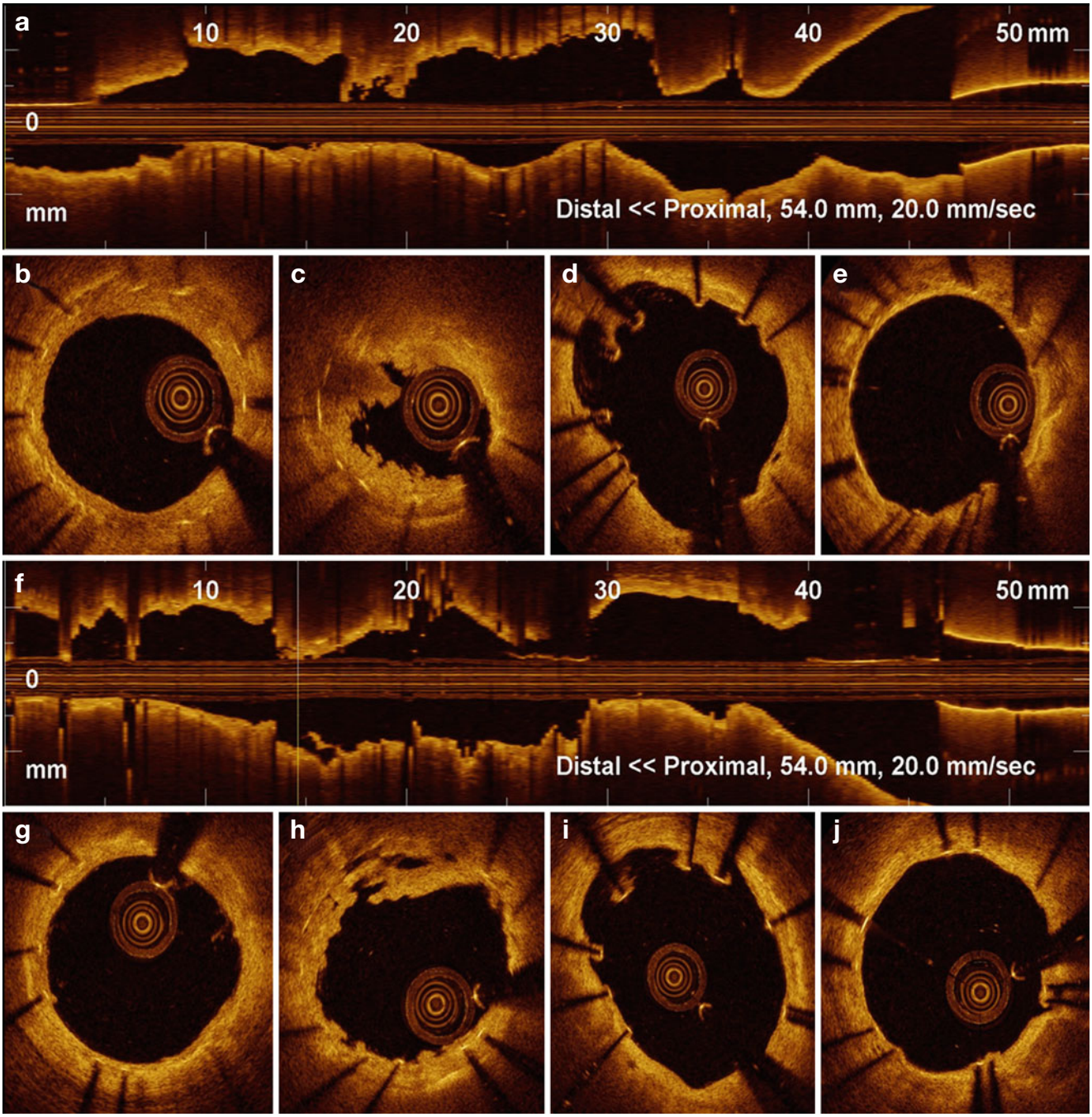


Fig. 11.3 OCT in Late Stent Thrombosis, Immediately After Thrombus Aspiration. OCT Longitudinal view (**a**) and multiple cross-sections (**b**–**e**) images obtained in very late stent thrombosis, immediately after manual thrombus aspiration. Large residual thrombus is observed inside the stent, dominantly white in signal characteristics (**c**). Struts malapposition can be observed (**d**). Same vessel after intracoronary injection of GP IIb/IIIa inhibitors. A substantial reduction of the remaining thrombus can be recognized in long (**f**) and cross-sectional (**h**) images. Incompleteley apposed stent struts can be identified in the cross sections proximal to thrombus burden (**d**, **i**). Healthy looking distal (**g**) and proximal (**j**) stent segment

Illustrative Case 2

Persistent Malapposition as Causative Factor of Stent Thrombosis

Brief summary: Two everolimus-eluting-stent (EES) were implanted to treat an occluded left descending coronary artery (LAD) during an anterior STEMI. The proximal stent was bordering a small aneurysm (arrow, Fig. 11.7). After 4 years, the patient was urgently hospitalized due to a recurrent anterior STEMI. Coronary angiography showed a thrombotic occlusion at the stent entrance. After wiring the occluded vessel and an effective manual thrombus aspiration, coronary angiography displayed only a small filling

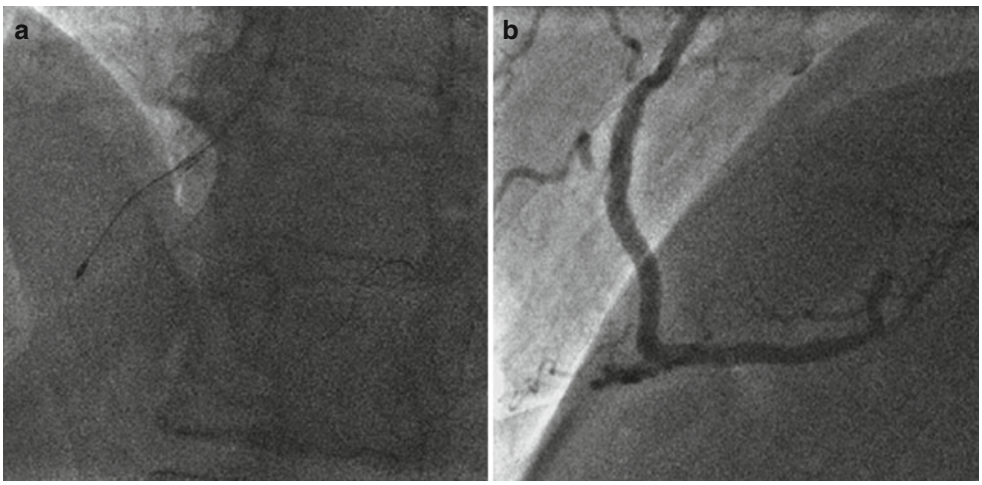


Fig. 11.4 Coronary angiography at the index procedure. (**a**) Rotational atherectomy at mid RCA. (**b**) Optimal result after DES implantation

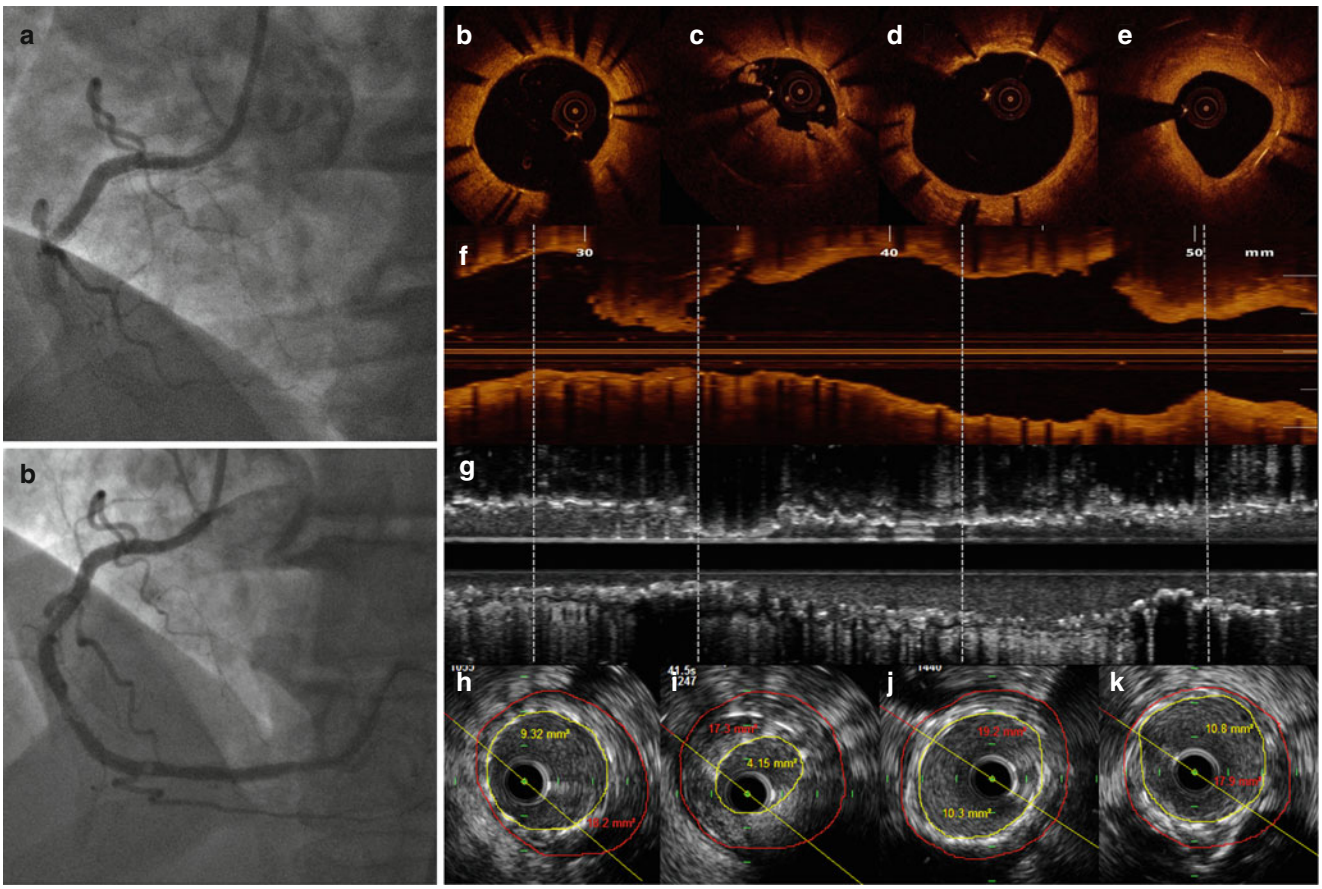


Fig. 11.5 OCT and IVUS findings at time of very late ST. (**a**, **b**) coronary angiography showing stent thrombosis at mid RCA (**a**) and lumen profile after reestablishing of the vessel patency with thrombus aspiration (with small persisting filling defects). (**b**, **d**, **e**) OCT cross sectional views at multiple levels. Distal and proximal stent segments demonstrated complete strut coverage, no malposition and only mild tissue deposition (**e**). (**c**) OCT cross section with stent under-expansion at the site of protruding thrombus, remaining after manual aspiration. The thrombus was not detected at the corresponding IVUS section (**i**). (**f**, **g**) Longitudinal OCT and IVUS views. Distal (**h**) and proximal (**j**, **k**) to the culprit lesion (**i**) IVUS cross sectional images, show good stent expansion and moderate vessel remodeling

defect, with irregular borders at the level of a small aneurysm (Fig. 11.8). An IVUS pullback, sequentially performed after OCT, excluded the presence of positive vessel remodeling, confirming the persistent nature of malapposition. Large malapposition associated with lack of coverage was identified as the causative mechanism in this EES ST (Fig. 11.9). To further expand the entrance of the existing stent, and promote the strut coverage in this small aneurysm, a large BMS was implanted at malapposition site and finally expanded at high pressure (Fig. 11.10).

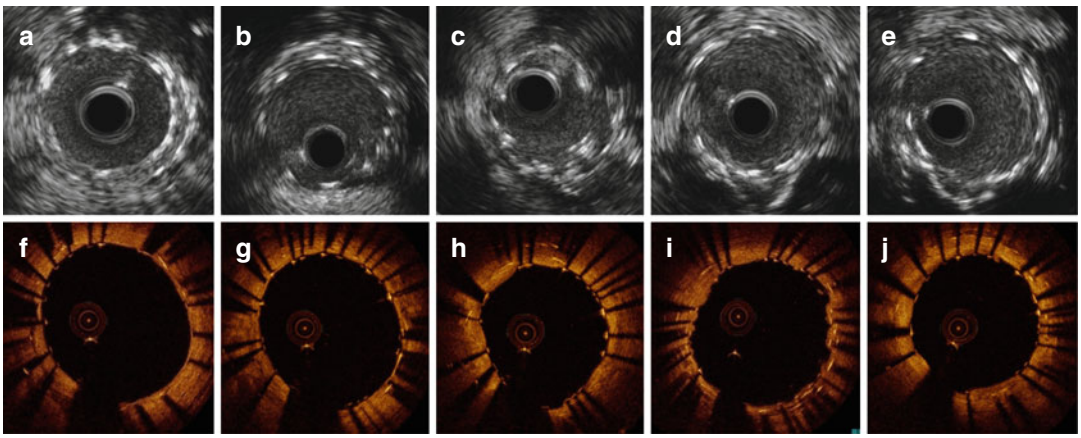


Fig. 11.6 IVUS and OCT assessment post-treatment. (**a**–**e**) IVUS and (**f**–**j**) OCT multiple cross-sectional views. Large MLA, even at site of multiple strut layers

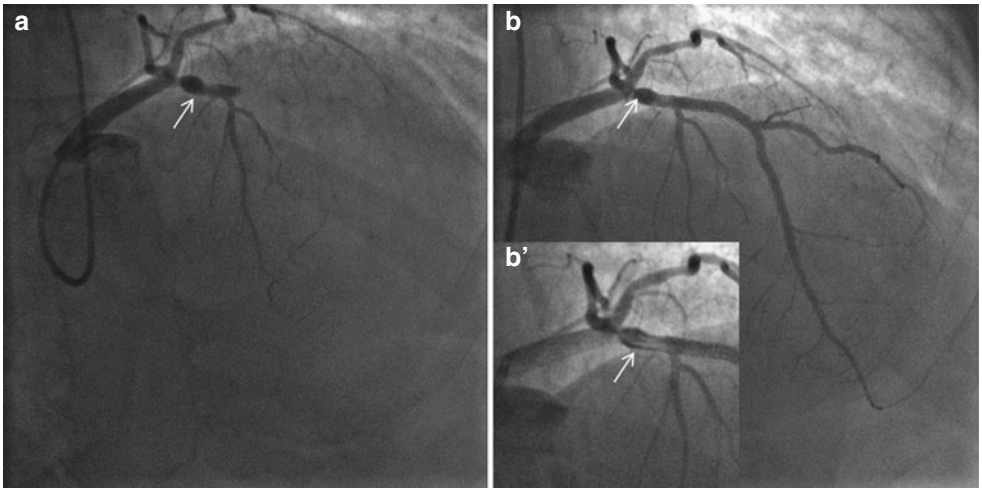


Fig. 11.7 Index primary PCI on LAD during an anterior STEMI. (**a**) Coronary angiography at the index procedure (primary PCI) with LAD occlusion. A small aneurysm was visible (*arrow*) immediately before the occlusion point. (**b**) Coronary angiography immediately after stent implantation with a reestablished lumen profile and effective coronary flow. (**b**') Magnification at the stented segment with evidence of contrast staining bordering the small aneurysm (*arrow*)

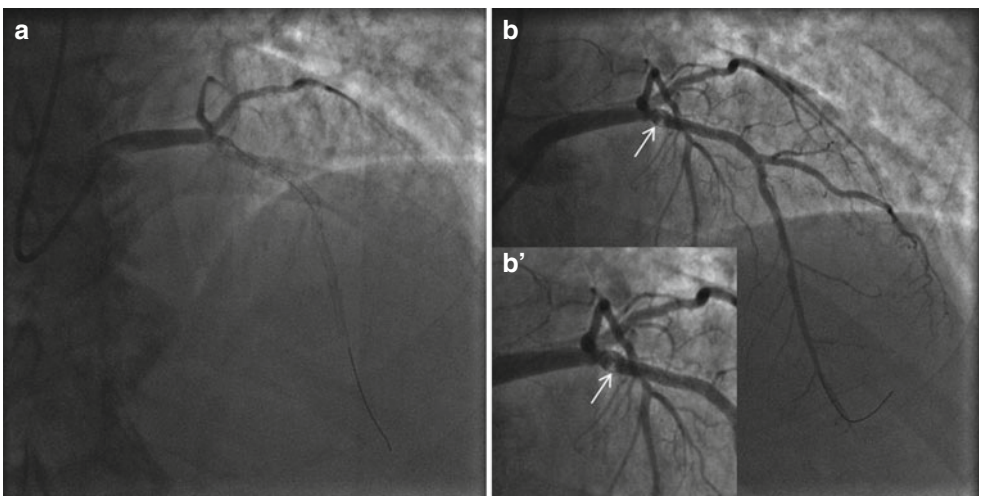


Fig. 11.8 Coronary angiography performed during very late ST. (**a**) Coronary angiography showing an in stent thrombotic occlusion. (**b**) After thrombus aspiration and restored vessel patency. (**b**') Magnification at proximal LAD after thrombus aspiration: persistent haziness at the level of the aneurysm located at the stent entrance (*arrows*)

This case shows some of the issues with stent implantation during acute myocardial infarction, when the presence of thrombus and the increased vasoconstriction make difficult the stent size selection and the identification of the proper landing zone, facilitating stent malapposition to remain undetected by angiography. In such cases a large segment of malapposed/uncovered struts may persist asymptomatic for years until a triggering factor may precipitate ST.

Finally, as demonstrated by Gutierrez-Chico and coll., the larger the acute malapposition, the greater the likelihood of persistent malapposed segments at FU and delayed healing [47].

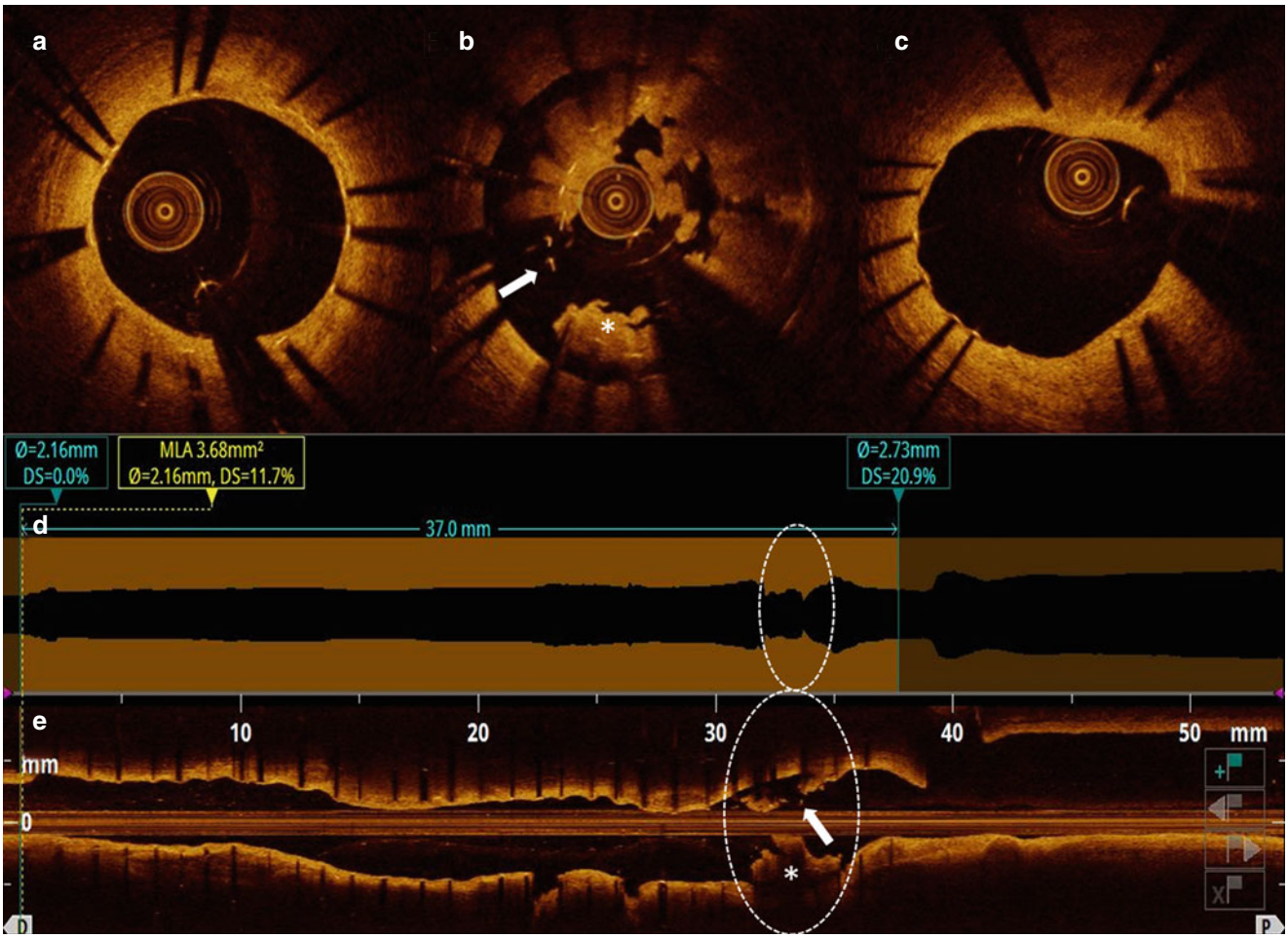


Fig. 11.9 OCT longitudinal and cross-sectional views after thrombus aspiration. Cross-sectional views: (**a**, **c**) optimal healing and coverage of the stented segment at both distal and proximal sites. (**b**) Cluster of grossly malapposed and uncovered struts (*arrow*) with large remaining thrombus (*). Automatic lumen border detection (**d**) and long view (**e**) showing overall uniform and good stent expansion, except for the segment at the aneurysm level (*circle*)

Illustrative Case 3

Acquired Malapposition in Current Generation DES as Cause of Stent Thrombosis

A 50 year old man presented with an anterior STEMI and cardiogenic shock. The proximal LAD was then treated by implantation of a 3.5/24 mm everolimus eluting stent (Fig. 11.11). Two months later, despite an adequate DAPT, the patient experienced recurrent chest pain and was admitted with diagnosis of non ST elevation myocardial infarction (NSTEMI). Coronary angiography revealed invariable stenosis in the left circumflex artery (LCX) and a barely noticeable in stent hazy lesion in the previous stented LAD. Fractional Flow Reserve (FFR) investigation of LCX resulted in a non-ischemic value. OCT revealed uncovered and malapposed stent struts, and a luminal protruding mass combining the characteristics of both organized and fresh thrombus (Fig. 11.12). The diagnosis of late ST as the culprit lesion was therefore made. Interestingly, the MULTIPLATE analyzer testing platelet reactivity revealed sufficient platelet inhibition by ongoing therapy. Thus the hypothesis of persistent or acquired ISA, was considered as the possible substrate for this complication. Application of high pressure balloon (4.5/12 mm at 20 atm) dilatation resulted in a larger cross-section area and corrected stent apposition (Fig. 11.13).

This case illustrates that secondary thrombus resolution in the contest of STEMI may cause ST due to acquired stent malapposition even in patients responsive to DAPT therapy. The use of OCT helped in the identification of mechanisms underlying ST and guided a customized treatment with a high pressure balloon dilatation. Combined use of imaging technology with platelet reactivity tests are sometimes needed to detect the mechanism underlying ST events.

ISA after stent implantation may also present with acquired in-stent aneurysm(s) formation and largely uncovered/malapposed struts. This results mainly from a toxic reaction to a drug and/or polymer creating extensive coronary wall inflammation with in stent extra-cavities formation. The segment involved has a significant damping of the

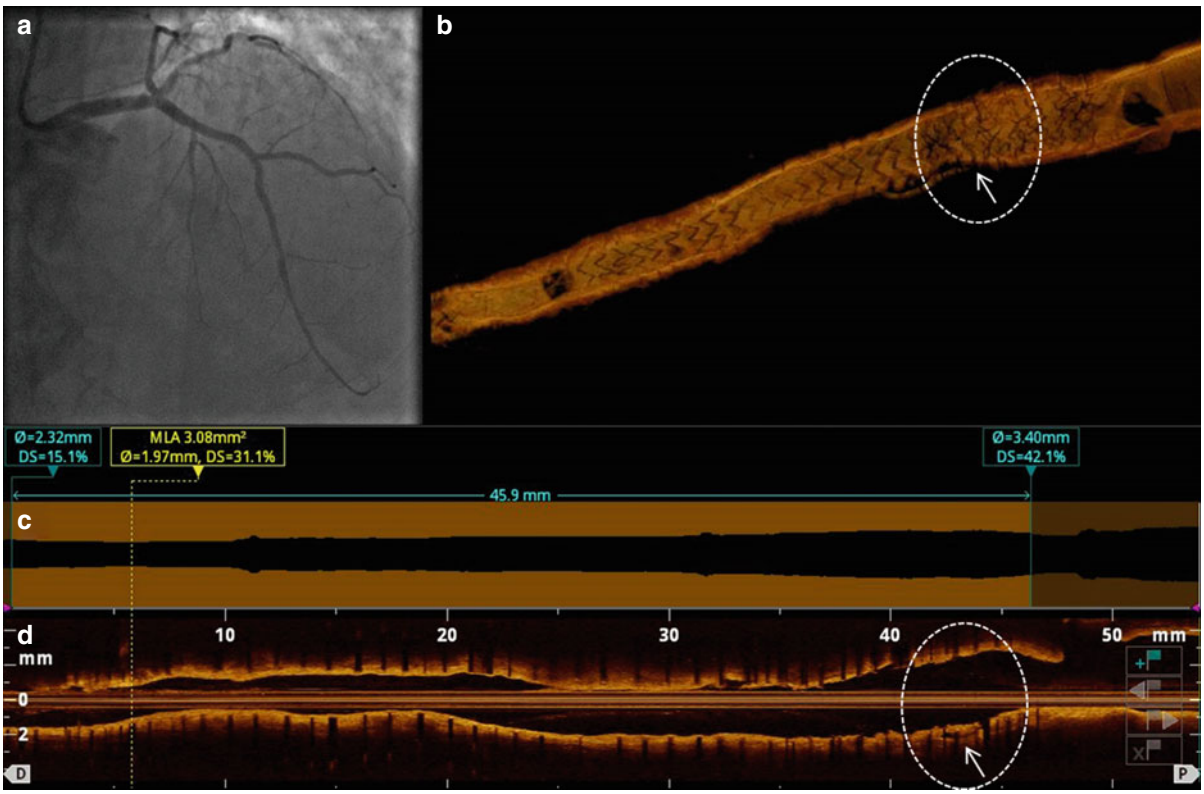
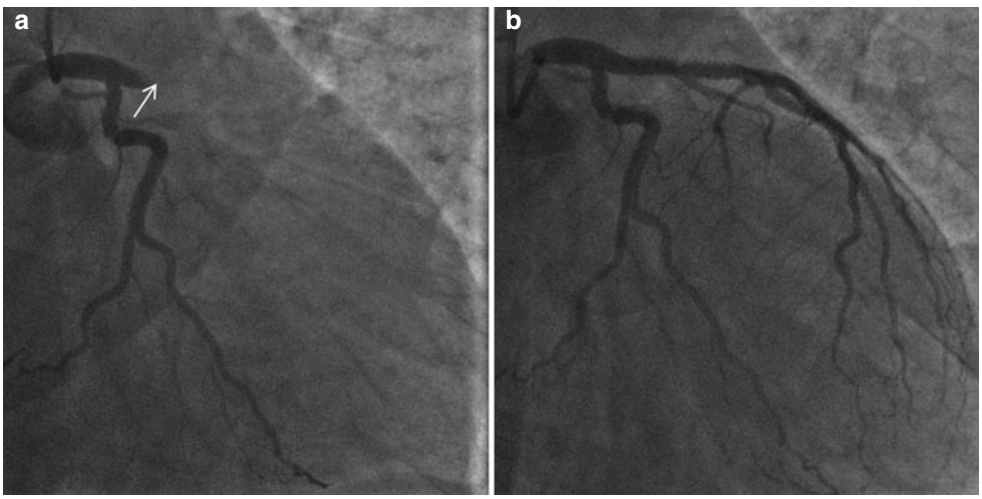
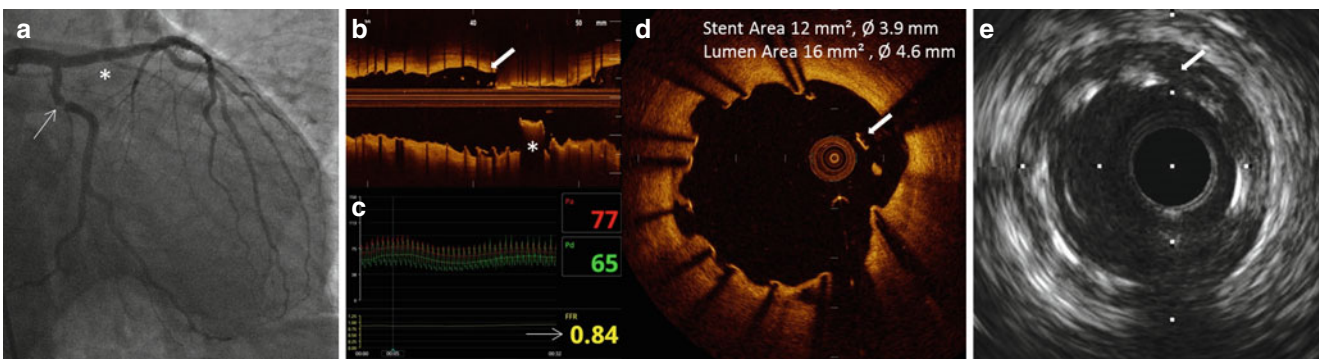


Fig. 11.10 OCT pullback after BMS implantation at the malapposed site. Coronary angiography (**a**) and OCT at post-treatment. The 3D OCT reconstruction (**b**), automatic lumen profile (**c**) and longitudinal view (**d**) confirmed optimal stent expansion with no residual malapposition (*arrow*) in the segment of interest (*circle*)

Fig. 11.11 Baseline procedure. (**a**) Coronary angiography during index primary-PCI showed thrombotic occlusion of left anterior descending artery (*arrow*). (**b**) Coronary angiography after stent implantation showing acceptable result





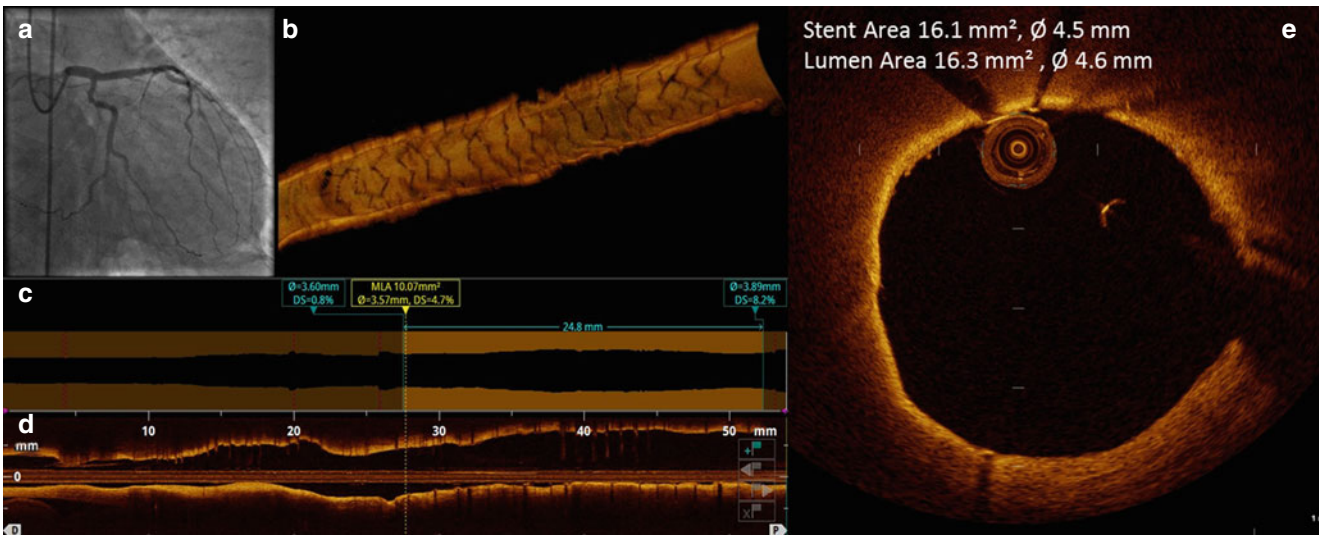


Fig. 11.13 OCT pullback after high pressure dilatation. (**a**) Final coronary angiography demonstrated good angiographic results of high pressure balloon dilatation. (**b**) 3D OCT reconstruction showed perfect result with optimal stent strut geometry; (**c**, **d**) Lumen profile tool and longitudinal reconstruction did not revealed residual stenosis and stent edge dissection after high pressure balloon stent expansion. (**e**) Cross-section analysis at the proximal stent edge showed resolution of the strut malapposition

optical signal (dark segmental appearance) compared to the uninvolved segments that normally have a mature neointima. These aspects were recently substantiated in an OCT study assessing different degrees of maturity on top of the stent struts, in various preclinical and clinical contexts (*ex-vivo* animals and humans, and *in-vivo* animals and humans) [48].

Illustrative Case 4

Very Late Stent Thrombosis due to Late Acquired Malapposition

Fifty-seven years old male presenting with multi-vessel coronary artery disease was treated with PCI and two PES implanted in overlap on the proximal LAD. Three years later the patient was readmitted for an anterior STEMI in cardiogenic shock complicated by cardiac arrest. Emergency angiography, under external cardiopulmonary resuscitation, documented very late ST on the proximal LAD, prompt balloon dilation immediately restored vessel patency. Extracorporeal support (ECMO) was immediately initiated. A few days later, with haemodynamic stability, an OCT pullback displayed the presence of an acquired in-stent aneurysm with extra-cavities around the entire circumference of the vessel, and largely uncovered and malapposed struts (Fig. 11.14). As treatment, a PCI with a bare metal "stent in stent implantation" was performed in an attempt to promote strut coverage and seal these extra-cavities. The patient was then discharged on the 30th day with complete left ventricular function recovery. At the 6 months OCT follow-up a complete sealing of the in-stent aneurysm with homogeneous stent coverage was observed (Fig. 11.15).

11.9.4 Uncovered Struts

Uncovered struts, the most important pathologic predictor of late and very late ST following DES placement, can be identified by OCT with high specificity, [49]. However, the sensitivity of OCT in detecting uncovered struts is reduced when fibrin and inflammatory cells are present around the struts. Uncovered struts are an indirect marker of delayed stent healing and poor endothelialization, more frequently observed in DES compared to BMS, [50]. Uncovered struts detected by OCT in DES may persist for several years and, in line with pathology data, may be an independent factor for predicting late and very late ST [43]. Compared with matched uneventful patients, ST patients showed a significantly higher percentage of uncovered struts and a higher number of sections with >30 % uncovered struts. Interestingly, the length of the segment with consecutive uncovered struts was the only OCT predictive factor for ST selected at the multivariate analysis. Similarly, the MOST [45] study demonstrated that the number and percentage of uncovered stent struts were particularly high at the site of ST, with similar values to pathological findings. However, it is still unknown

Fig. 11.12 Angiographic and OCT findings of late stent thrombosis. (**a**) Coronary angiography shows an area of haziness inside the EES previously implanted in the left anterior descending artery (*), and a tight focal stenotic lesion in mid circumflex artery (*arrow*). (**b**) Longitudinal reconstruction after thrombus aspiration revealed the thrombotic nature of the intraluminal hazy lesion (*). (**c**) FFR performed on circumflex artery was negative (**d**) close review of cross-section OCT reveals clusters of uncovered and malapposed struts. (**e**) IVUS pullback revealed absence of positive vessel remodeling and free space behind stent struts

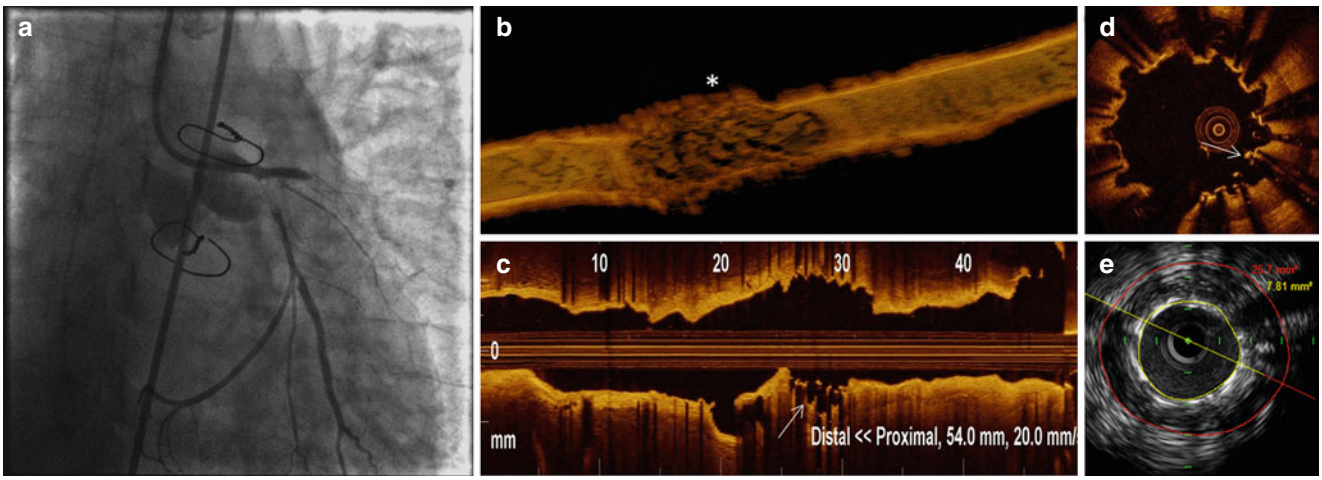


Fig. 11.14 Coronary angiography, OCT and IVUS during very late ST with cardiac arrest. (**a**) Coronary angiography during cardiac arrest showing thrombotic occlusion of proximal LAD and LCX. (**b**) 3D OCT reconstruction after primary-PCI and hemodynamic stabilization revealed a segmental in-stent aneurysm at site of overlap (**asterisk*). (**c**, **d**) Long view OCT and cross section analyses showed clusters of uncovered and malapposed struts (*arrow*). (**e**) IVUS pullback confirmed large positive remodeling at the stent overlap, (*arrow*).

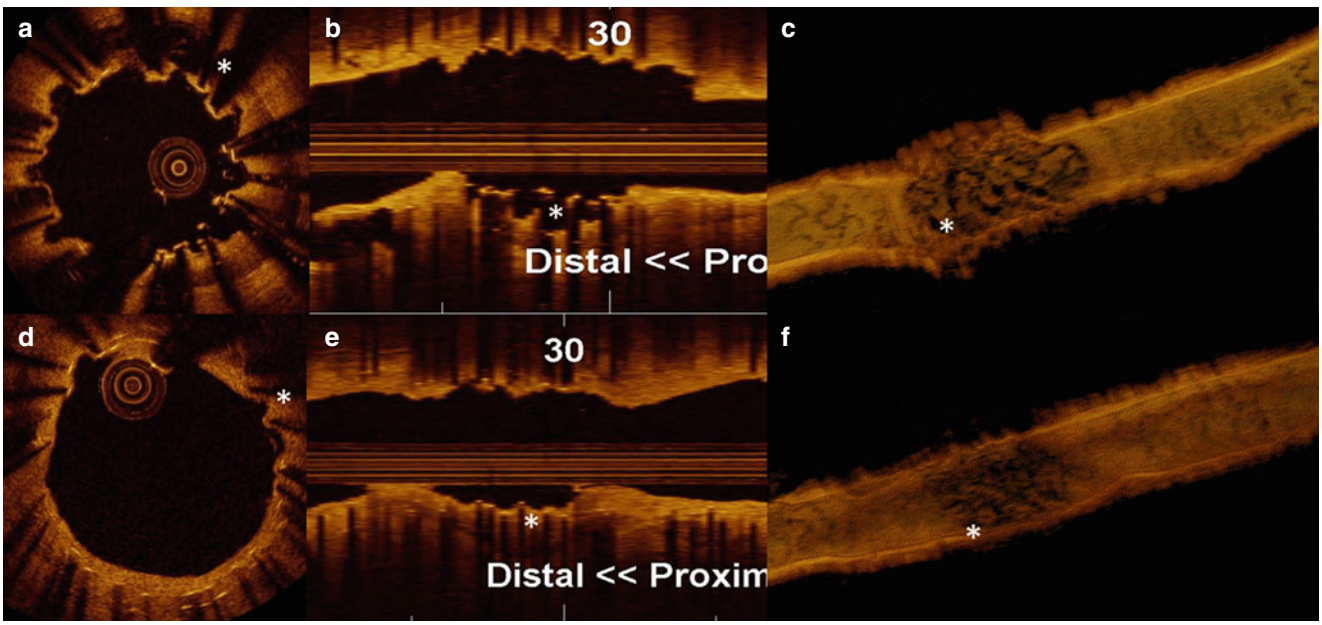


Fig. 11.15 Post PCI with BMS OCT Findings after very late ST. (**a**–**c**) cross section, longitudinal and OCT 3D reconstruction after very late ST with localized in-stent extra cavities and largely uncovered/malapposed struts at the stent overlap (**asterisk*). (**d**–**f**) OCT findings 9 months after focal BMS implantation (**asterisk*). showing sealing of the in-stent extra-cavities with complete strut coverage

which extent of lack of struts coverage promotes ST and should be considered unsafe. In the absence of any additional factor(s), the presence of uncovered struts is probably acting only as a risky substrate, requiring a precipitating factor to trigger thrombus formation, [51]. This hypothesis has been substantiated by the fact that many uncovered stents remain asymptomatic for years. Coverage of the stent struts depends also on the underlying plaque composition. Lüscher et al. demonstrated that DES implantation in lesions with a large necrotic core might result in delayed endothelialization or absent healing [52]. This observation is consistent with the OCT finding reported by Guagliumi et al. which showed that acute coronary syndrome at the index procedure was more frequently observed in patients with ST as compared with the controls [43].

Uncovered struts may be found in several circumstances:

(a) Uncovered struts due to malapposition to the vessel wall at time of initial implant
(b) Uncovered struts due to acquired malapposition, secondary to positive vessel remodeling
(c) Uncovered struts in the presence of a stent completely apposed to the vessel wall (inadequate healing)

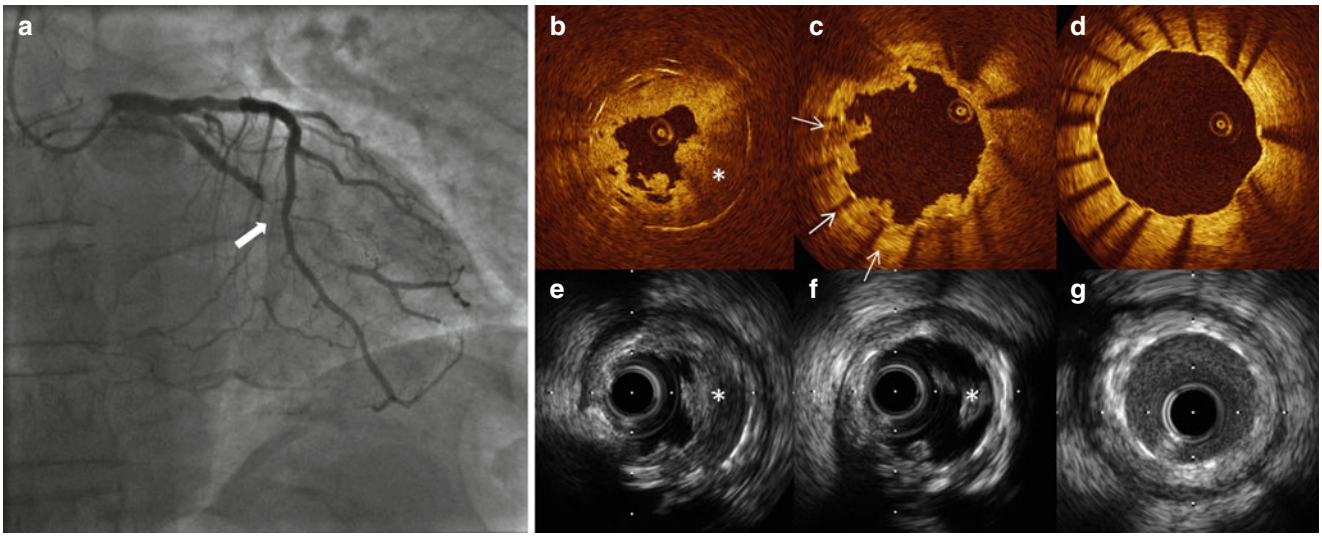


Fig. 11.16 Role of isolated uncovered struts promoting ST. (**a**) Coronary angiography after thrombus aspiration (*arrow*); (**b–d**) cross sections substantiate stent thrombotic occlusion (**b** *), thrombus attached on top of uncovered stent struts (**c**-*arrows*); (**d**) uniform tissue coverage of the stent in the proximal segment. (**e–g**) corresponding IVUS cross-sections obtained with contrast flushing to enhance lumen visualization with no evidence of positive remodeling

The association with different types of malapposition has already been discussed and presented in prior clinical cases. The following figure reports a clinical example of the role of isolated uncovered struts promoting ST even in the presence of a stent completely apposed to the vessel wall (Fig. 11.16).

11.9.5 Neoatherosclerosis

Neoatherosclerosis is pathologically recognized as clusters of lipid pools within the neointima, representing the entire spectrum from lipid rich plaque with or without necrotic core, to TCFA with foamy macrophages, to plaque rupture and calcium deposition [40]. Optical imaging techniques contributed in a substantial way to the identification and characterization of this abnormal neointima growth as a possible causative factor for ST. With intracoronary angioscopy, Higo et al. observed a 35 % increase of intra-stent yellow neointima, 10 months after DES implantation and hypothesized that neoatherosclerosis within the stent might serve as a possible substrate for late ST [53]. At OCT images, lipid-laden neointima, compared to non-lipid stent segments, is more frequently associated with intimal disruption, neovascularization and thrombus formation, all possibly implied in late ST [54]. Guagliumi et al. found that in 17 % of late/very late ST in DES patients (median time from initial stent implant being 20 months) neoatherosclerosis was the likely mechanism [43]. Kang et al. recently demonstrated from a series of 33 patients suffering from very late ST that neoatherosclerosis was the primary mechanism in almost 70 % of patients (median time from initial stent implant being 62 months), while malapposition was observed in only 25 % of all cases [44]. The frequency of the in-stent neoatherosclerosis is time dependent and is not normally observed as a consistent finding until approximately 1.5–2 years post-DES implantation [55].

Illustrative Case 5

Very Late Stent Thrombosis due to Neoatherosclerosis

A 63 year old male previously treated with two PES on LCX-OM, and LAD was readmitted 4 years later for NSTEMI. Coronary angiography showed a complete occlusion of both the LCX and OM branches (Fig. 11.17). After manual thrombus aspiration, OCT pullback revealed an heterogeneous vessel response in the stents implanted in the LCX. In-stent segments with lipid laden neointima with segments presented a lack of tissue coverage. More specifically, lipid laden neointima presented patterns of light attenuation and bright lines with an important shadow suggestive of foamy macrophage accumulation at the culprit segment (Fig. 11.18). A current generation DES was implanted in the segment with significant stenosis, but not the whole segment that presented lipid laden neointima (Fig. 11.19).

Despite the fact that neoatherosclerosis is a well-known phenomenon in first generation DES, recent reports have demonstrated that this in stent abnormal tissue proliferation may also be involved in new generation DES [56].

11.9.6 Other Mechanisms Involved in Stent Thrombosis

ST may be also the consequence of other mechanisms including disease progression at the stent edges, plaque rupture underneath the stent, poor responsiveness to DAPT, or a combination of multiple causative factors.

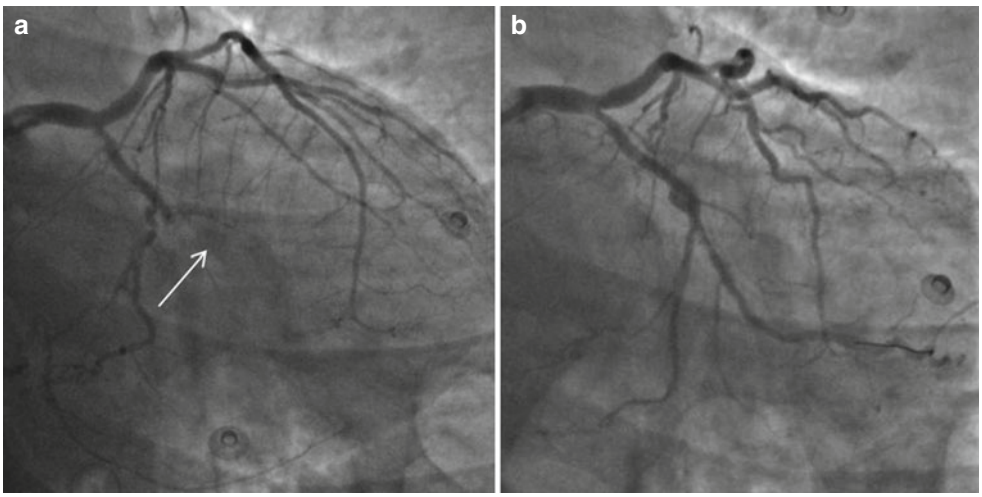


Fig. 11.17 Coronary angiography at time of very late stent thrombosis. (**a**) Coronary angiography: in stent thrombotic occlusion of the marginal obtuse branch (*arrow*); (**b**) After thrombus aspiration and restoration of vessel patency

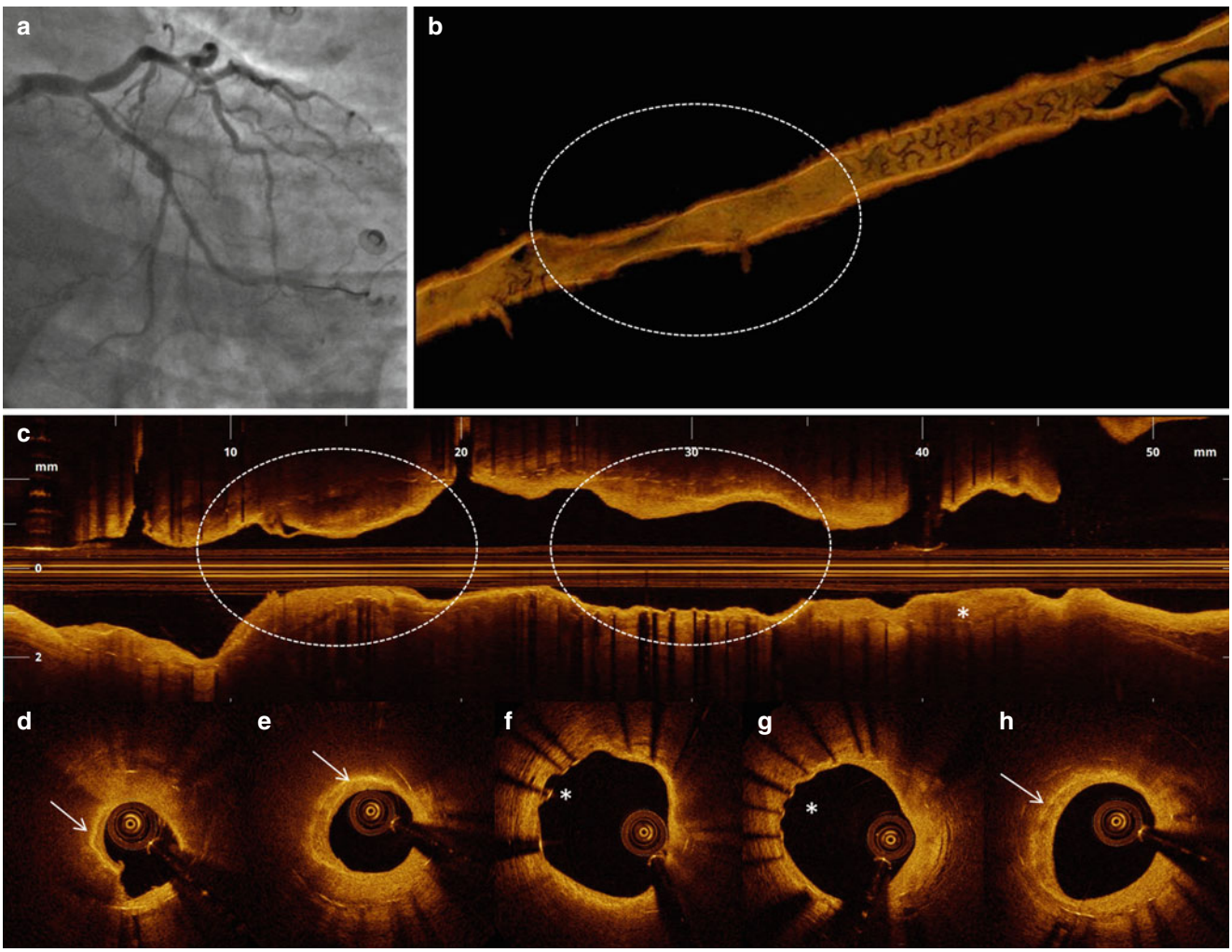


Fig. 11.18 OCT findings of the in-stent neoatherosclerosis. (**a**) Coronary angiography after thrombus aspiration; (**b**, **c**) 3D and Longitudinal OCT view displayed multiple in-stent segments infiltrated by lipid laden neointima (*circle*). Cross sections substantiate different patterns of coexisting lipid infiltration within the stent lipid rich plaques (**d**, **e**, **h**), signals of foamy macrophage accumulation (**d**, **e**, **h**-*arrows*) and uncovered stent struts (**f**, **g**-*)

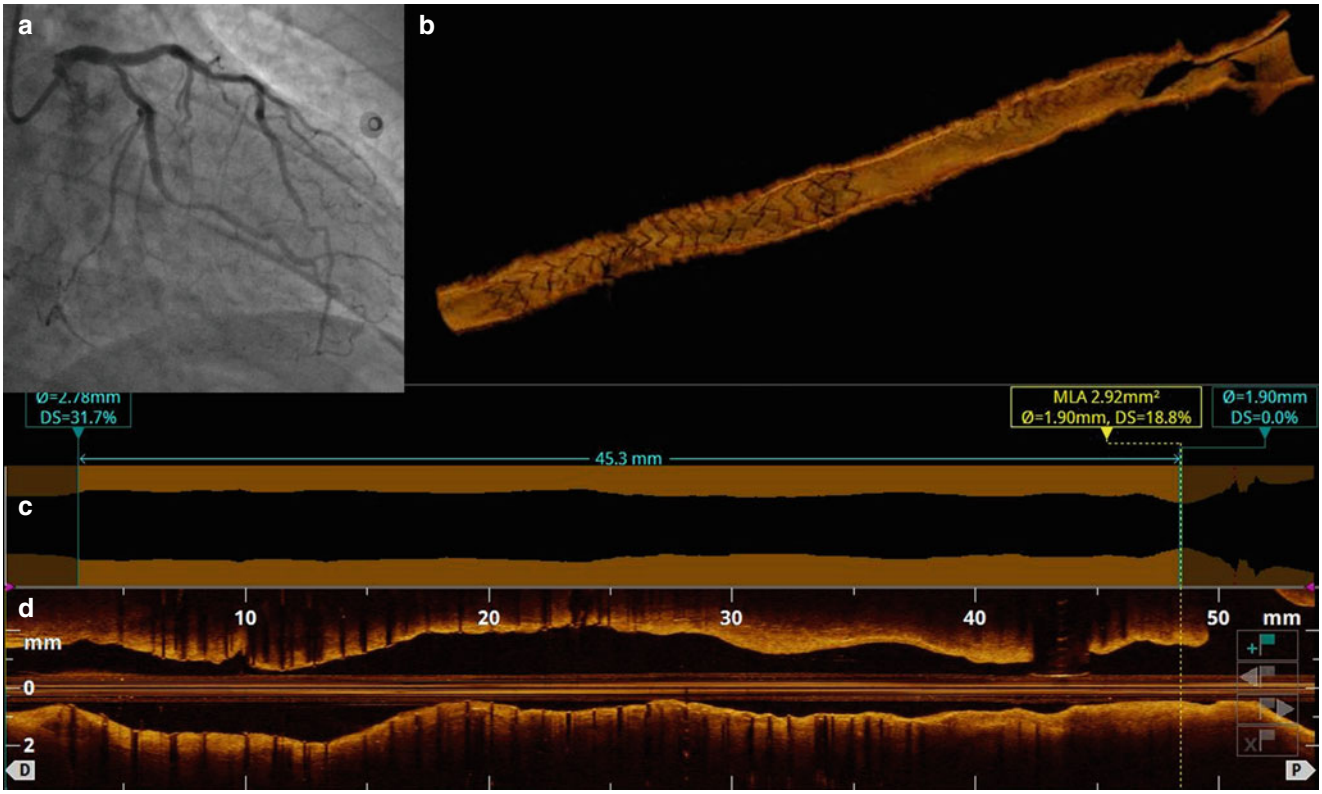


Fig. 11.19 Final angiography and OCT images after novel generation EES implantation. (**a**) Coronary angiography after the implantation of a current generation EES stent. (**b**) 3D OCT reconstruction with optimal stent strut geometry and no cell deformation; (**c**, **d**) automatic lumen border and longitudinal views displayed uniform stent in stent expansion, no residual stenosis and no stent edge dissection after high pressure stent expansion

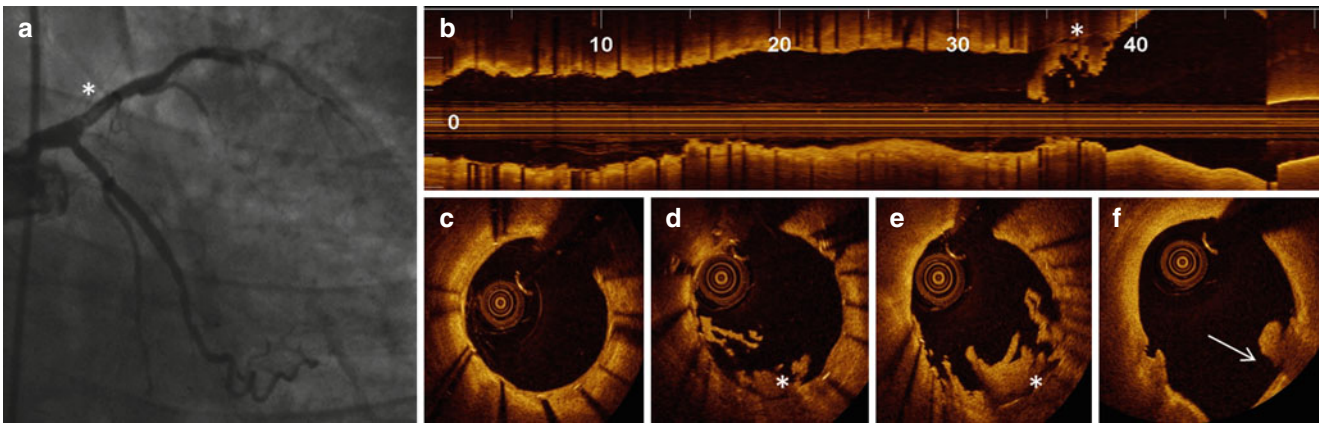


Fig. 11.20 Coronary angiography and OCT during very late ST. (**a**) Coronary angiography showing haziness and filling defect at the proximal LAD (* *asterisk*). (**b**) OCT longitudinal view: optimal result of the previously implanted PES with complete strut coverage and protruding thrombus at the LAD ostium (**asterisk*). (**d**, **e**) White thrombus tail extending into the proximal stent edge (*). (**f**) Ruptured plaque located at the ostium of the LAD at the stent proximal edge (*arrow*)

Illustrative Case 6

Rupture Plaque at the Edge of the Stent as Causative Factor of Late ST

A 88-years old man with stable angina received 2 PES in the proximal LAD. After 2 years the patient was readmitted with an anterior STEMI. At the time of coronary angiography the LAD was opened, with a filling defect at the proximal stent entrance. OCT revealed complete strut coverage with minimal neointimal deposition across the entire stented segment. A white thrombus on top of a new ruptured plaque at the ostium of the LAD was easily detected by OCT (Fig. 11.20). New ruptured plaque was sealed by an additional EES

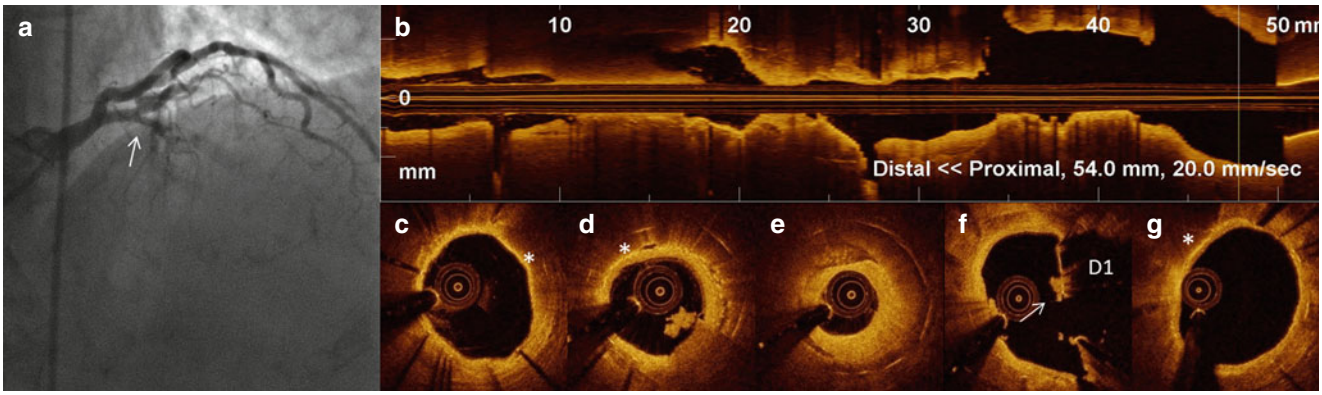


Fig. 11.21 Angiographic and OCT images during primary PCI performed for very late ST. (**a**) coronary angiography before thrombus aspiration showed a thrombotic stent occlusion at proximal LAD, involving the first diagonal branch (*arrow*). (**b**) OCT long view demonstrated an irregular lumen contour with some degree of stenosis and atherosclerotic lipid laden neointima. (**c**–**g**) cross sectional views from the distal to the proximal stent segments. (**c**, **g**) the cross sections at the stent edges showed an early pattern of neoatherosclerosis with thin cap lipid rich plaques and foamy macrophage (*). (**d**, **e**) Body of the stents presenting with more advanced stages of neoatherosclerosis with mixed thrombus (**d**- 4–6 o'clock) and calcified plaque (**e**- 10–12 o'clock). (**f**) cross-section at the level of the D1 bifurcation showing stent under-expansion and cell strut deformation (*arrow*)

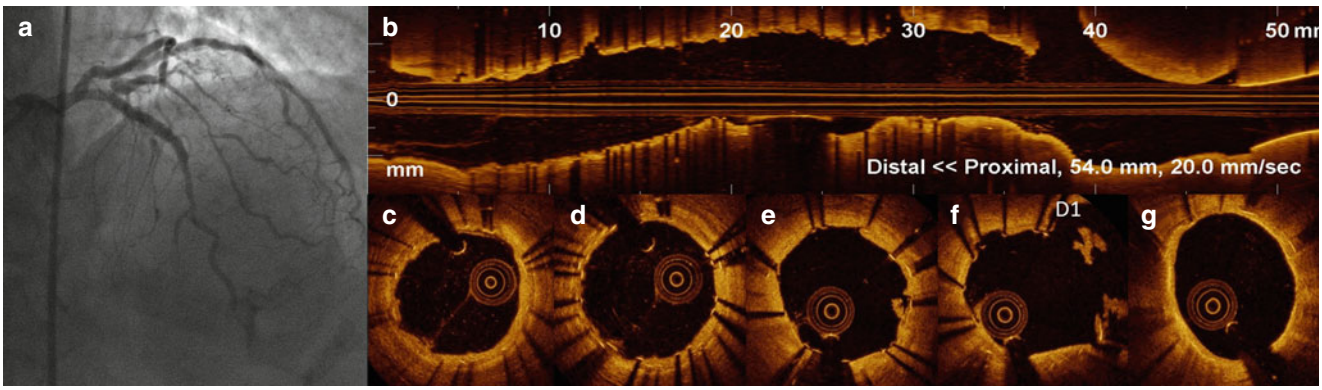


Fig. 11.22 Angiography and OCT after treatment. (**a**) Final coronary angiography with no residual stenosis and TIMI 3 flow grade. (**b**) Longitudinal OCT view showing a large lumen area across the entire stented segments, with no residual stenosis and no stent edge dissection. (**c**–**g**) OCT cross-sectional views confirming complete stent expansion, a full compression of the lipid laden neoitima and a wide access to the *D1* branch (**f**)

implanted at the ostial LAD. Progression of disease at the inflow/outflow tract can be responsible for late DES failure. Late ST may be observed even in the presence of an optimal DES result, with complete stent healing.

Illustrative Case 7

ST with Coexisting Multiple Causative Factors

Due to its high level of accuracy OCT can detect multiple mechanisms implicated in ST at the same time. In the following case ST was associated with the presence of stent under-expansion and geometry deformation at the bifurcation lesion, combined with atherosclerotic neointima deposition. A 63-year old patient had two PES implanted in the proximal LAD, as provisional stents across the LAD-first diagonal (D1). bifurcation. Five years later the patient was readmitted to the hospital with an anterior STEMI. Coronary angiography showed a complete occlusion at the stent entrance, with TIMI 0 flow grade. The flow was reestablished with thrombus aspiration performed in both branches. OCT detected multiple coexisting causative factors bystanders, with lipid laden neointima (*) and calcium deposition (arrow) in some cross sections, severe stent deformation and under-expansion with fragments of thrombus in other sections (Fig. 11.21).

Current generation EES were implanted inside the two PES, and post-dilated at high pressure. A final OCT pullback confirmed the full lumen/stent expansion, the absence of any remaining stent deformation and wide open access to D1 (Fig. 11.22).

11.10 Limitations of OCT Imaging During Stent Thrombosis

Whenever thrombus is present, a reliable assessment of strut coverage with OCT during ST is difficult. Current OCT cannot differentiate between neointimal and other tissue types.

Endothelial cell dimensions are below the resolution of even OCT, and it is possible that some struts that appear bare in fact is covered by a thin layer of tissue. Futhermore, ST it cannot be excluded that thrombus aspiration might have partially removed this thin layer of material covering the stent struts. Moreover OCT, unlike IVUS cannot always provide information on vessel size (media to media), and therefore is not possible to judge the presence of a stent under expansion and vessel remodeling.

11.11 New Perspectives for in Stent Thrombosis

The low frequency occurrence of ST with paucity of sparse data collected by different interventional groups and the possible catastrophic clinical consequences of this complication has attracted the attention of the Heath Care Authorities to have a more global approach to solve this problem. Therefore, very large cohorts of ST patients need to be recruited in order to substantiate the main mechanisms involved and to possibly demonstrate the impact of a given intervention. Moreover, the evaluation of patients with ST needs to include a comprehensive evaluation using combined clinical, high resolution intracoronary imaging, blood platelet function data and genes. Large-scale clinical trials with long-term follow-up as well as detailed mechanistic assessments are warranted. In pursuit of these goals, the "PREvention of Stent Thrombosis by an Interdisciplinary Global European effort" PRESTIGE project, supported by a financial grant of the EU Community (FP7-Seventh Health Program, Health 2010.2.4.2-1, Reducing in-stent thrombosis) represents an advanced and unique multidisciplinary project, involving world –leading European specialists and centers, in the study of all the contributing factors to ST in five different working packages. The five fields of actions in the PRESTIGE project are: (1) Assessment of the basic mechanisms leading to ST (2) Bio-engineering approaches to reduce ST (3) Novel imaging approaches to assess healing and thrombotic processes after stenting (4) Multimodal characterization of patients with late ST (5) Exploitation of the results. In this project the PRESTIGE-registry (WP4) is the joint effort to collect data regarding all patients presenting with ST. An extensive clinical and procedural database, integrated with blood platelet functional tests, OCT/IVUS intracoronary imaging, DNA-sampling and histopathological and immunohistochemical analyses of aspirated thrombus was prospectively collected. Between April 2011 and April 2014, all patients with angiographic confirmed ST were enrolled into the PRESTIGE Registry, in 14 centers and compared to control patients without ST who underwent a PCI with stent implantation on the same date (±14 days) and with the same indication. At present more than 200 consecutive ST were assessed with OCT (±IVUS) combined with histopathology of aspirated thrombus. The PRESTIGE project is anticipated to result in significant improvement in the understanding, prediction and treatment of ST, providing surrogate marker(s) identification and tailored therapeutic and interventional strategies.

Conclusions

The occurrence of ST is rare; however it remains one of the most dreadful complications following PCI, due to potential catastrophic clinical events. The prevention of ST represents a major challenge in interventional cardiology, due to the multiple causative and contributing factors. The limited value of coronary angiography in differentiating causative factors responsible for ST has been recently updated/ameliorated by with the amazingly informative content of OCT, detecting thrombus, plaque, tissues and stent components. The use of OCT in the acute phase of ST, when the flow has been reestablished, allows to promptly identifying the main causative mechanisms (incomplete stent expansion, uncovered/malapposed struts, toxic vessel response with extra-cavities formation, disease progression, neoatherosclerosis). Furthermore, by addressing the implicated mechanisms, OCT may allow individualized treatment through targeted mechanical or pharmacological interventions. Finally, the use of OCT at different time points of follow-up after ST allows for the unique opportunity to verify the long term vessel response (coverage, sealing of in-stent aneurysm), and possibly reduce the risk of ST recurrences.

References

1. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al.; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. N Engl J Med. 2004;350(3):221–31.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al.; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003;349(14):1315–23.
3. Kuchulakanti PK, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, et al. Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation. 2006;113(8):1108–13.
4. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007;369(9562):667–78.
5. Cook S, Meier B. Have we been misled by the ESC DES firestorm? EuroIntervention. 2008;3(5):535–7.
6. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al.; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344–51.
7. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, et al. Angiographic follow-up after placement of a self-expanding coronary-artery stent. N Engl J Med. 1991;324(1):13–7.

8. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation. 1995;91(6):1676–88.
9. Karrillon GJ, Morice MC, Benveniste E, Bunouf P, Aubry P, Cattan S, et al. Intracoronary stent implantation without ultrasound guidance and with replacement of conventional anticoagulation by antiplatelet therapy. Circulation. 1996;94(7):1519–27.
10. Moussa I, Di Mario C, Reimers B, Akiyama T, Tobis J, Colombo A. Subacute stent thrombosis in the era of intravascular ultrasound-guided coronary stenting without anticoagulation: frequency, predictors and clinical outcome. J Am Coll Cardiol. 1997;29(1):6–12.
11. Schühlen H, Kastrati A, Dirschinger J, Hausleiter J, Elezi S, Wehinger A, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. Circulation. 1998;98(2): 104–11.
12. De Servi S, Repetto S, Klugmann S, Bossi I, Colombo A, Piva R, et al. Stent thrombosis: incidence and related factors in the R.I.S.E. Registry (Registro Impianto Stent Endocoronarico). Catheter Cardiovasc Interv. 1999;46(1):13–8.
13. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, Carrozza Jr JP, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation. 2001;103(15):1967–71.
14. Ong AT, Hoye A, Aoki J, van Mieghem CA, Rodriguez Granillo GA, Sonnenschein K, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. J Am Coll Cardiol. 2005;45(6):947–53.
15. van Werkum JW, Heestermans AA, de Korte FI, Kelder JC, Suttorp MJ, Rensing BJ, et al. Long – term clinical outcome after a first angiographically confirmed coronary stent thrombosis: an analysis of 431 cases. Circulation. 2009;119(6):828–34.
16. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Jüni P, Vaina S, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study. J Am Coll Cardiol. 2008;52(14):1134–40.
17. Moreno R, Fernández C, Hernández R, Alfonso F, Angiolillo DJ, Sabaté M, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. J Am Coll Cardiol. 2005;45(6):954–9.
18. Kastrati A, Dibra A, Eberle S, Mehilli J, Suárez de Lezo J, Goy JJ, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. JAMA. 2005;294(7):819–25.
19. Sarno G, Lagerqvist B, Fröbert O, Nilsson J, Olivecrona G, Omerovic E, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J. 2012;33(5):606–13.
20. Palmerini T, Kirtane AJ, Serruys PW, Smits PC, Kedhi E, Kereiakes D, et al. Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. Circ Cardiovasc Interv. 2012;5(3):357–64.
21. Holmes Jr DR, Kereiakes DJ, Garg S, Serruys PW, Dehmer GJ, Ellis SG, et al. Stent thrombosis. J Am Coll Cardiol. 2010;56(17): 1357–65.
22. Iakovou I, Schmidt T, Bonizzoni E, Sangiorgi GM, Stankovic G, Airoldi F, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA. 2005;293(17):2126–30.
23. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009;53(16):1399–409.
24. Kohn CG, Kluger J, Azeem M, Coleman CI. Short-term consequences of angiographically-confirmed coronary stent thrombosis. PLoS One. 2013;8(10):e77330.
25. Parodi G, Memisha G, Bellandi B, Valenti R, Migliorini A, Carrabba N, et al. Effectiveness of primary percutaneous coronary interventions for stent thrombosis. Am J Cardiol. 2009;103(7):913–6.
26. Chechi T, Vecchio S, Vittori G, Giuliani G, Lilli A, Spaziani G, et al. ST-segment elevation myocardial infarction due to early and late stent thrombosis a new group of high-risk patients. J Am Coll Cardiol. 2008;51(25):2396–402.
27. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, et al. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA. 2011;306(11):1215–23.
28. Rinaldi MJ, Kirtane AJ, Piana RN, Caputo RP, Gordon PC, Lopez JJ, et al. Clinical, procedural, and pharmacologic correlates of acute and subacute stent thrombosis: results of a multicenter case-control study with 145 thrombosis events. Am Heart J. 2008;155(4):654–60.
29. de la Torre-Hernández JM, Alfonso F, Hernández F, Elizaga J, Sanmartin M, Pinar E, et al. ESTROFA Study Group. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). J Am Coll Cardiol. 2008;51(10):986–90.
30. Roy P, Torguson R, Okabe T, Pinto Slottow TL, Steinberg DH, Smith K, et al. Angiographic and procedural correlates of stent thrombosis after intracoronary implantation of drug-eluting stents. J Interv Cardiol. 2007;20(5):307–13.
31. Park DW, Park SW, Park KH, Lee BK, Kim YH, Lee CW, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. Am J Cardiol. 2006;98(3):352–6.
32. Pinto Slottow TL, Bonello L, Gavini R, Beauzile P, Sushinsky SJ, Scheinowitz M, et al. Prevalence of aspirin and clopidogrel resistance among patients with and without drug-eluting stent thrombosis. Am J Cardiol. 2009;104(4):525–30.
33. Gurbel PA, Bliden KP, Samara W, Yoho JA, Hayes K, Fissha MZ, et al. Clopidogrel effect on platelet reactivity in patients with stent thrombosis: results of the CREST Study. J Am Coll Cardiol. 2005;46(10):1827–32.
34. Nakano M, Yahagi K, Otsuka F, Sakakura K, Finn AV, Kutys R, et al. Causes of early stent thrombosis in patients presenting with acute coronary syndrome: an ex vivo human autopsy study. J Am Coll Cardiol. 2014;63(23):2510–20.
35. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation. 2004;109(6):701–5.
36. Nebeker JR, Virmani R, Bennett CL, Hoffman JM, Samore MH, Alvarez J, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol. 2006;47(1):175–81.
37. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006;48(1):193–202.
38. Cook S, Ladich E, Nakazawa G, Eshtehardi P, Neidhart M, Vogel R, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation. 2009;120(5): 391–9.
39. Park SJ, Kang SJ, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol. 2012;59(23):2051–77.
40. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011;57(11):1314–22.
41. Mintz GS. Clinical utility of intravascular imaging and physiology in coronary artery disease. J Am Coll Cardiol. 2014;64(2):207–22.

42. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Expert's OCT Review Document. Eur Heart J. 2012;33(20):2513–20.
43. Guagliumi G, Sirbu V, Musumeci G, Gerber R, Biondi-Zoccai G, Ikejima H, et al. Examination of the in vivo mechanisms of late drug-eluting stent thrombosis: findings from optical coherence tomography and intravascular ultrasound imaging. JACC Cardiovasc Interv. 2012;5(1):12–20.
44. Kang SJ, Lee CW, Song H, Ahn JM, Kim WJ, Lee JY, et al. OCT analysis in patients with very late stent thrombosis. JACC Cardiovasc Imaging. 2013;6(6):695–703.
45. Parodi G, La Manna A, Di Vito L, Valgimigli M, Fineschi M, et al. Stent-related defects in patients presenting with stent thrombosis: differences at optical coherence tomography between subacute and late/very late thrombosis in the Mechanism Of Stent Thrombosis (MOST) study. EuroIntervention. 2013;9(8):936–44.
46. Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation. 2007;115(18): 2426–34.
47. Gutiérrez-Chico JL, Wykrzykowska J, Nüesch E, van Geuns RJ, Koch KT, Koolen JJ, et al. Vascular tissue reaction to acute malapposition in human coronary arteries: sequential assessment with optical coherence tomography. Circ Cardiovasc Interv. 2012;5(1): 20–9.
48. Malle C, Tada T, Steigerwald K, Ughi GJ, Schuster T, Nakano M, et al. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. Arterioscler Thromb Vasc Biol. 2013;33(6):1376–83.
49. Nakano M, Vorpahl M, Otsuka F, Taniwaki M, Yazdani SK, Finn AV, et al. Ex vivo assessment of vascular response to coronary stents by optical frequency domain imaging. JACC Cardiovasc Imaging. 2012;5(1):71–82.
50. Guagliumi G, Costa MA, Sirbu V, Musumeci G, Bezerra HG, Suzuki N, et al. Strut coverage and late malapposition with paclitaxel-eluting stents compared with bare metal stents in acute myocardial infarction: optical coherence tomography substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial. Circulation. 2011;123(3):274–81.
51. Zwart B, van Werkum JW, Heestermans AA, Kelder JC, Zomer AC, van't Hof AW, et al. Triggering mechanisms of stent thrombosis. EuroIntervention. 2011;6(6):722–8.
52. Lüscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation. 2007;115(8): 1051–8.
53. Higo T, Ueda Y, Oyabu J, Okada K, Nishio M, Hirata A, et al. Atherosclerotic and thrombogenic neointima formed over sirolimus drug-eluting stent: an angioscopic study. JACC Cardiovasc Imaging. 2009;2(5):616–24.
54. Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. J Am Coll Cardiol. 2009;55(1): 26–32.
55. Yonetsu T, Kim JS, Kato K, Kim SJ, Xing L, Yeh RW, et al. Comparison of incidence and time course of neoatherosclerosis between bare metal stents and drug-eluting stents using optical coherence tomography. Am J Cardiol. 2012;110(7):933–9.
56. Otsuka F, Vorpahl M, Nakano M, et al. Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211–23.