Coronary angiography is the gold standard for establishing the presence, location, and severity of epicardial coronary artery lesions, and to guide interventional procedures. This imaging method has the unique value to limit the complex three-dimensional (3D) atherosclerotic pathology to a single, simple, and easy-to-be-used parameter: the percent reduction of the lumen profile. However, the resolution limits of coronary angiography, combined with more demanding precision during percutaneous interventions, fueled the research and development of high-resolution intracoronary imaging techniques. Currently available intracoronary imaging systems allow a much higher level of in vivo accuracy, with fine vessel wall details and measures. Sound and light sources were used to penetrate the entire vessel wall structure or to obtain high-resolution details in the field near the lumen. Intravascular ultrasound (IVUS) and angioscopy came first to bring additional information regarding plaque mass and thrombus presence, respectively. Optical coherence tomography (OCT) combines the luminal details of angioscopy with the tomographic capabilities of IVUS. Due to its enhanced micron scale resolution, a precise delineation between the lumen and the vessel wall is achieved, making highly reproducible quantifications of 360° of the investigated segment possible. In addition, novel FD-OCT (frequency domain OCT) allows a full scan of the entire vessel in only 2 to 3 seconds, without vessel occlusion. As a consequence, minimum diameters and areas, reference segments, and stenosis are instantaneously available after a single pullback (Figure 1). The discriminating power of OCT allows accurate optical imaging to optimize stent evaluation and outcomes.

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Figure 1. FD-OCT assessment of the coronary artery before and after implantation. Automated contour detection algorithm for assessment of the severity and extension of the coronary atherosclerotic pathology and assessment of acute results after percutaneous coronary intervention. Longitudinal reconstructions of the coronary artery, detecting the length of the lesion (A) and cross-sectional analysis of the severity with relative healthy reference segments (B and D) and severe pathology (C). Longitudinal reconstruction of the same artery after stent implantation (A1), with cross-sectional data showing stent apposition (B1 to D1) and minimum cross-sectional area (C1).
identification of the intravascular environment, whether it is a healthy vessel or varying stages of coronary artery disease. OCT can be performed before procedures and after interventions. A preprocedure OCT obtains detailed information on the segmental extent of the atherosclerotic pathology (lesion length, plaque nature, presence and depth of calcification, thrombus formation). OCT imaging performed after stent implantation allows an accurate assessment of the stent expansion and strut apposition. At follow-up, OCT is able to evaluate the degree and completeness of stent coverage and the tissue vascular responses. OCT can be performed in either stable or unstable patients, including cases of acute myocardial infarction.

**VESSEL ASSESSMENT IN ELECTIVE INTERVENTIONS**

The more complex the planned intervention is, the more useful the information obtained by intracoronary imaging can be. A higher sensitivity and specificity of OCT for tissue components of coronary plaques, including fibrotic, calcified, and lipid-rich plaques, have been reported compared with integrated grayscale or backscatter IVUS. In addition, OCT interpretation does not require the same level of expertise as IVUS, with a shorter learning curve and more clear-cut separation among images. Detailed assessment and measurement of the pathology’s extent with OCT may overcome the foreshortening or elongation effects observed with some angiographic views, whereas tomographic evaluation of the entire vessel unravels the coronary pathology hidden by planes in overlap. Knowing the true extent of the atherosclerotic disease helps in selecting the appropriate stent length, whereas precise reference vessel assessment may avoid geographic miss, including stent undersizing or significant edge dissection, variables highly correlated with poor clinical outcomes (Figure 2). The identification of plaque type with OCT before a procedure may bring prognostic implications. Recently reported clinical cases prove preprocedural OCT’s unique ability to avoid late drug-eluting stent (DES) failure, revealing at the landing zone the presence of inflamed, lipid-rich core plaques, undetected by angiography and causing focal restenosis. Furthermore, OCT may quantitatively assess the amount of lipid content in plaques that correlates with the risk of distal embolization during PCI.

In calcified tissue, the ability of OCT to penetrate calcium (a major limitation of IVUS) and quantify distribution (arc of circumference) and depth of calcium accumulation into the vessel wall may be used for planning rotational atherectomy debulking (Figure 3). If a main bifurcation is approached, OCT may allow careful assessment of the disease anatomy, including the risk of plaque shift at the carina level, based on side branch takeoff angle and plaque distribution. If rewiring of the stent implanted in the main vessel is required to gain access to a side branch ostium, OCT may...
help in detecting where the wire should be placed to avoid stent distortion. All of these unique features are pivotal for planning interventional strategy and choosing the right tools to provide adequate results with minimal complication rates (Figure 4). Novel software upgrades with 3D capabilities may be superior for clinical decision making compared with the conventional longitudinal or cross sectional views.

VESSEL ASSESSMENT IN ACUTE CORONARY SYNDROMES

In acute coronary syndrome (ACS), disrupted or fissured plaques and thrombus deposition are normally present. Angiography has intrinsic limits in delineating the content and severity of the culprit lesion in ACS patients. Conversely, in the presence of irregular and eccentric lesion borders, OCT can easily detect all of these pathologic components and differentiate them from spontaneous coronary dissection, intramural hematoma, or erosion of the plaque (Figure 5).9 The use of OCT in the culprit vessel of acute myocardial infarction (AMI) was able to show the in vivo presence of multiple vulnerable plaques,10 supporting the value of a combined interventional and pharmaceutical strategy with high-dose statin and fast-acting antiplatelet agents. OCT’s ability to accurately detect thrombus formation is high and comparable to that of coronary angioscopy,11 but with the added advantage of a full tomographic vessel scan, which is not possible with angioscope. Based on light backscattering and signal attenuation, OCT may differentiate thrombus composition.12 Red cell-rich thrombi (a mesh of fibrin and trapped erythrocytes) have an OCT appearance of highly intense tissue protrusion into the lumen, with rapid signal attenuation and shadowing. Platelet-rich thrombi (white thrombi) are signal-rich protruding or lining masses with minimum attenuation (Figure 6). These optical tissue characteristics may allow thrombus age approximation. The benefit of thrombus removal in patients with AMI and ACS has been clearly demonstrated in randomized prospective trials.13 Adjunctive manual thrombectomy was associated with better epicardial and myocardial perfusion, less distal embolization, and significant reduction of 30-day mortality. In this respect, OCT can add precise and semiquantitative assessment of the residual amount of thrombus after aspiration. Prati et al were able to demonstrate that by using an OCT thrombus score in patients with ACS undergoing PCI, the local delivery of GP IIb/IIIa inhibitors was more effective in thrombus removal compared with intracoronary bolus of abciximab and downstream administration of clopidogrel.14 Two major ongoing prospective OCT trials in STEMI patients (TROPHY and OCTAVIA) are dealing with various aspects of thrombus removal in the culprit AMI vessel. These studies using volumetric reconstruction of the thrombus burden may help to define the effectiveness and limits of current thrombus aspiration strategies.

STENT EVALUATION

Stent Assessment at Implantation

OCT is able to provide information on vessel, plaque, and stent interactions.15 Optimal stent implantation has always been of importance to interventional cardiologists. During the bare-metal stent (BMS) era, the main reason...
to maximize the final result was to limit the amount of neo-intimal growth; in the current DES era, the major concern is minimizing the risk of stent thrombosis. Immediately after stent implantation, accurate evaluation of stent expansion and symmetry, malapposed struts, and the remaining pathology at the landing zone, may provide information for optimal PCI results. By using serial OCT, Ozaki demonstrated that incomplete stent apposition (ISA) observed at follow-up in sirolimus-eluting stents (SES) is more frequently derived from postintervention persistent ISA, rather than acquired ISA due to vascular remodeling. A cutoff value of ISA that can affect negative outcomes is still to be established in prospective studies. However, Shite et al recently reported 400 µm of distance between the strut and the vessel wall (approximately four times the thickness of the current generation DES) as the threshold for persistent malapposition in follow-up, with minimal probability of sealing. However, the relationship between these OCT findings and the long-term clinical outcome remains unknown.

In complex bifurcation, OCT is able to assess strut distortion and lack of coverage at the side branch ostium, in addition to strut malapposition (Figure 4). A relatively high proportion of incompletely apposed struts were reported after stent deployment in calcified lesions, even at a high pressure. OCT segmental delineation of calcific plaques is more accurate than IVUS. Finally, OCT may reveal injuries to the vessel resulting from stent placement, including plaque disruption, protruding tissue, edge dissection, and new thrombus formation. Although these OCT findings are frequently observed after stenting, recent studies showed that these non-flow-obstructing defects were not normally associated with abnormal vascular response and adverse outcomes.

**Stent Assessment at Follow-Up**

Assessing the vascular responses to DES implantation at follow-up may help to stratify the risk of future adverse clinical events. Multiple OCT imaging variables are currently under scrutiny.
Uncovered struts. The use of DES has markedly reduced the rate of restenosis observed with BMS. Intramural delivery of potent cell-cycle inhibitors via DES polymer blocks smooth muscle cell migration and proliferation in response to vessel injury. Thus, the amount of tissue covering DES is minimal (Figure 7A) and largely under the limit of resolution of both IVUS and coronary angiography. Selected human pathology specimens have identified the rate and clustering of uncovered and malapposed stent struts as the most potent independent predictor of late stent thrombosis (LST), a complication that involves 0.4% to 0.6% per year of all patients treated with first-generation DES. The unique value of OCT performed immediately after thrombus aspiration in patients with STEMI and definite LST was recently reported. In this study, 78% of all patients with definite LST exhibited uncovered struts and the frequency of cross-sections with largely uncovered struts (> 30% of the total) was 26.7% compared with less than 5% in asymptomatic matched controls from previous OCT studies. Although uncovered struts and ISA have been reported in asymptomatic patients after DES implantation, the clustering of uncovered/malapposed struts in consecutive stent segments plays an important role in facilitating LST. A recent coregistered ex vivo optical frequency domain imaging (OFDI)-histology study highlights the excellent sensitivity and specificity of OCT for detecting strut tissue coverage (Figure 7B). These data have been confirmed by in vivo preclinical studies comparing OCT images with scan electron microscopy, the gold standard for detecting tissue growth. Despite its unique accuracy in measuring stent tissue deposition, current OCT technology still has clear limitations in differentiating tissue types, while endothelial cells are below its current resolution capabilities.

Incomplete stent apposition. The role of ISA in stent thrombosis continues to be debated. IVUS studies have suggested that LST in SES is associated with positive vessel remodeling and acquired malapposition. However, the in vivo vascular response to different DES varies substantially. While LST in SES may be associated with high eosinophil content into the vessel wall and occlusive thrombus, medial necrosis and smooth muscle cell loss resulting in arterial dilation, stent malapposition, and excessive fibrin deposition are more frequently observed in LST after PES.

Serial OCT images, collected at different time points after paclitaxel DES implantation, suggested a very dynamic process with formation of newly malapposed areas and resolution of previously existing ones, occurring at different sites of the same stented vessel. The time frame between stent implantation and 3 months was the most active period, when the largest number of incompletely apposed struts at implantation resolved, while new areas of stent malapposition and aneurysm developed. Interestingly, the time period between 3 and 9 months was marked by an almost complete resolution of early acquired ISA but with the appearance of late ISA at completely new sites (Figure 7C).

Stent-related hypersensitivity and vascular toxicity. Local hypersensitivity and marked toxic vessel responses have been identified as causal factors of DES LST. Nondegradable polymers have been implicated in these processes. The optical characteristics of inflamed tissue surrounding the stent are quite unique. Local hypersensitivity and vessel toxicity is associated with irregular cavity formation around the struts and damped optical signal, compared with the intense bright signal of uniform coverage in the normal adjacent stented segments.

OCT has the potential for recognizing local vessel toxicity, enabling a comprehensive detection of multiple causes of DES ST and planning of adequate treatment strategies. The possibility of predicting the risk of stent thrombosis or guiding a dual-antiplatelet regimen based on OCT characteristics remains challenging. Large prospective data collection and more advanced software for tissue characterization are required. Despite the current limits, OCT has enormous potential to contribute to the refinement and evolution of new stent generations, including fully absorbable DES.

Residual thrombus. Additional OCT findings that may herald late adverse events in stented patients include detection and quantification of a thrombus. OCT is extremely sensitive and accurate in thrombus detection and characterization. Pathological studies have shown an association between lack of strut coverage and intraluminal thrombus formation. This association has been confirmed in vivo by OCT and coronary angiography, which identified an increased incidence of “thrombus-like” tissue in vessels treated with first-generation DES, particularly in patients undergoing stent implantation during ACS.

Fibrin. The distinction between fibrin deposition and mature neointima remains a primary goal of the novel OCT technologies—to limit the unnecessary prolonged use of dual-antiplatelet therapy in all DES-treated patients. This goal was recently attempted by Nakano et al. In a combined OCT- and histology-validating study, the investigators reported a clear difference of the OFDI signal peak intensity between fibrin and neointima. The signal attenuation was significantly greater for fibrin than for normal neointima, which might help in identifying malapposed struts accompanied by extensive fibrin accumulation. When present, fibrin deposition around the struts had a relatively dark appearance with irregular texture and lumen border. Areas of fibrin accumulation were not accompanied by the
intense, bright, and linear signals normally attributed to foamy macrophages or cholesterol crystals (Figure 7D).

In-stent restenosis. Usually considered to be a benign process, severe in-stent restenosis can present as ACS or acute myocardial infarction.\textsuperscript{31} Different types of neointima were observed in SES restenosis.\textsuperscript{33} Furthermore, the presence of thrombus has been associated with in-stent restenosis, suggesting that neointimal hyperplasia developing after SES may lack antithrombotic properties. The atherogenic propensity of the neointima may also be involved, as described in dedicated OCT imaging studies.\textsuperscript{34}

In-stent neoatherosclerosis. In addition to delayed healing and local vascular toxicity, neoatherosclerosis may occasionally occur as a cause of LST. By using intracoronary angioscopy, Higo et al\textsuperscript{31} found a 35% increase of yellow neointima 10 months after DES implantation, suggesting a possible role of neoatherosclerosis as a different substrate for LST. Pathologic studies have confirmed accelerated atherosclerosis and plaque progression more commonly in DES compared with BMS.\textsuperscript{35} Although in BMS serially evaluated by OCT, a lipid-laden neointima, intimal disruption, and stent thrombosis were more frequently observed at long-term follow-up, these findings are developing earlier in DES. In-stent neoatherosclerosis with a lipid core has a layered OCT appearance with dark areas inside the growing neointima, frequently colocalized with intense bright signals, suggesting the presence of foamy macrophages and/or cholesterol crystals. In such cases, additional imaging findings that may help to differentiate neoatherosclerosis include neovessels and cavity formation (Figure 7E).

CONCLUSION

OCT is a much more recent imaging technology compared with coronary angiography or IVUS. As such, multiple fields of application are still unexplored or not completely understood. However, the potential of this innovative imaging method is enormous based upon the flexibility of the light sources, the multiple parameters that might be used, and the expected margin of amelioration in lasers and optics. Now that a full scan of the vessel is possible in only 2 to 3 seconds, the more stringent priorities are in obtaining measurements and interpretation as fast as the acquisition time. With new advanced software, automatic 3D reconstruction with precise autodetection of vessel size, lesion length and dimension, and size and location of stent malapposition is possible. Coregistration with angiography will facilitate an immediate comparison between the simple, even if not specific, lumen profile of angiography and the extremely detailed, more informative OCT tomographic views. These technical advances promise to allow more precise and individualized PCI-guided interventions.

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