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Optical Coherence Tomography in the Era of Drug-Eluting Stents: An Indispensable Workhorse

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Undoubtedly, the breakthrough introduction of drug-eluting stents (DES) has nearly abolished the need for reintervention, accounting for nearly 10-15% need for target vessel revascularization (TVR) at long-term follow-up [1,2]. Indeed, the enthusiasm associated with the early results of first-generation DES let us believe that the long-standing concern inherent to percutaneous coronary intervention (PCI) has probably come to a pleasant end. After years 'in duty', however, worrisome reports have raised concerns about disturbingly high rates of late and very late (after one year) stent thrombosis associated with DES, that frequently culminates into myocardial infarction or, even more gravely, death [3]. Scaring enough, these reports launched a 'wake-up call' to carefully evaluate the likely mechanisms underlying this potentially life-menacing event. Insights from histopathological studies suggested that delayed neointimal coverage of DES struts - a built-in problem of these devices - was reasonably the first 'suspect' to condemn [4]. One more suspect was stent strut malapposition, again a favorable position for struts to remain 'nude' [5]. In the quest to 'see what is going on' *in vivo*, invasive imaging techniques were called into action. Intravascular ultrasonography (IVUS), the benchmark of these, did demonstrate a 10-20% incidence of strut malapposition associated with DES; almost double that reported following bare-metal stent implantation [6,7]. Unfortunately, however, the resolution of IVUS (100-200 μm) is clearly less sensitive to visualize slight degrees of strut malapposition, and rationally, far below that needed to reveal the ultrathin early - and healthy - neointimal layer covering stent struts. In this context, an advanced high-resolution imaging tool perfectly capable of portraying the vessel wall-lumen interface has long been awaited.

The recent appearance of coronary optical coherence tomography (OCT) in the clinical scene has, indeed, launched a new era in intravascular coronary imaging. Basically, OCT is a groundbreaking light-based imaging modality with an almost ten-fold higher resolution as compared with IVUS (axial 12-15 μm, lateral 20-40 μm). Having such an unparalleled high resolution with an outstanding contrast between the lumen and vessel wall, OCT is now offering a novel 'gold standard' for *in vivo* evaluation of coronary stents. Initially, a foremost downside was the need to temporarily clear blood off the field of view during OCT imaging. With first-generation OCT machines (the so called time-Domain OCT), this caveat limited the use of OCT to certain patient, and possibly, lesion categories, for its potential risk of inducing transient myocardial ischemia. Currently, this problem was generally overcome with the development of the second-generation (the so called Fourier-domain) OCT technology. In Fourier-domain OCT, a short-monorail OCT imaging catheter permits data acquisition at a world-record speed (frame rate 100/sec, pullback rate 20 mm/sec). Given such an unprecedented velocity, a 4-cm-coronary segment can be fully examined within a couple of seconds, in a user-friendly fashion, and without carrying the minimal risk of myocardial ischemia.

The unique feature about OCT is that it is capable of depicting with a high precision the zone of interface between the stent and the vessel wall, even at the level of individual struts. This is best exemplified evaluating the tiny neointimal stratum that eventually creeps to cover the struts following stent deployment. In this realm, OCT accurately demonstrates extremely thin neointimal layers over the struts, and can even measure their thickness with a high degree of reproducibility [8]. Providing this brand new 'surrogate endpoint', no wonder then that OCT was rigorously employed as an indispensable tool to evaluate subtle differences between various stent designs. Let's go through the following three examples. The multi-center randomized controlled LEADERS trial compared two members of the -limus-eluting stent family: a second-generation biodegradable-polymer biolimus-eluting stent and a first-generation durable-polymer sirolimus-eluting stent. In the original comparison, the former proved non-inferior to the latter regarding the occurrence of a composite of hard endpoints at 12-month follow-up [9]. Subsequently, an OCT substudy showed that the prevalence of uncovered struts at 9-month follow-up was less in the former as compared with the latter (0.7% versus 2.7%, respectively, p=0.04) [10]. The HORIZONS-AMI, another large-scale randomized trial compared DES (paclitaxel-eluting stents) with bare-metal stents in the setting of acute myocardial infarction undergoing primary percutaneous coronary intervention. It concluded that DES significantly reduced angiographic restenosis, with no increase in the safety endpoints at 12 months follow-up [11]. Yet, OCT revealed reduced neointimal hyperplasia, but significantly higher rates of uncovered struts associated with DES versus bare-metal stents at 13 months follow-up (5.7% versus 1.1%, respectively, p<0.0001) [12]. Third, the RESOLUTE All Comers trial compared two new-generation DES designs: a hydrophilic polymer-coated zotarolimus-eluting stent and a fluoropolymer-coated everolimus-eluting stent. In a population with minimal exclusion criteria, the former was non-inferior to the later for the occurrence of major cardiac adverse events at 12 months [13]. Eventually, OCT demonstrated that the rate of uncovered struts was similar between the two stent designs at 13 months follow-up (7.4% versus 5.8%, respectively, p=0.3) [14]. Excitingly, OCT was ultimately used to evaluate neointimal healing associated with bioabsorbable vascular stent scaffolds [15-17]. Unique information provided by OCT includes visualization of the structure of scaffold struts, exploration of neointimal coverage over time, and changes in the vascular tissue during the course of bioabsorption. Nevertheless, whether uncovered stent struts visualized by OCT directly relate to stent thrombosis seen late after PCI remains largely unclear. Furthermore, although having an outstanding resolution, the currently available OCT systems are far less sensitive to detect an isolated layer of endothelial cells. Hence, the absence of 'neointimal coverage' by OCT does not exclusively rule out stent strut endothelialization. The presence of a 'neointimal cover', on the other hand, is not a surrogate of an adequate endothelial function [18].

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Stent strut malapposition after PCI is another cause of growing concern in recent years, especially following PCI for acute coronary syndromes. Let's again review evidence available from large randomized controlled trials. In the LEADERS OCT substudy, the prevalence of malapposed struts at 9-month follow-up was quite lower with biolimus-eluting versus sirolimus-eluting stents (0.2% versus 0.5%, respectively, p=0.08) [10]. Meanwhile, significantly higher rates of malapposed struts were associated with paclitaxel-eluting stents as compared with bare-metal stents in the OCT substudy of the HORIZONS-AMI trial reported at 13 months follow-up (0.9% versus 0.1%, respectively, p=0.0003) [12]. Finally, the rate of malapposed struts in the OCT substudy of the RESOLUTE All Comers trial was similar between zotarolimus- and everolimus-eluting stents at 13 months follow-up (1.8% versus 1.4%, respectively, p=0.5) [14]. The figures reported by randomized controlled trials, however, seem quite idealistic owing to the standardized methodology and environment wherein these trials were conducted, and – even in the case of all-comers trials – might not truly reflect the real-world practice. Many stent struts ultimately remain malapposed – as demonstrated by OCT – even following post-dilatation with high-pressure balloons; this is especially frequent in regions of stent overlap [19]. The scene is further gloomy following stenting of complex coronary lesions with DES. In an interesting report, Tanigawa et al, [19,20] reported a rate of strut malapposition per lesion of 9.1 ± 7.4% associated with stent implantation in a variety of complex-type lesions [20]. Strikingly, univariate predictors of malapposition were the implantation of a sirolimus-eluting stent, the presence of overlapping stents, a longer stent length, and a type-C lesion. Potential explanations for stent strut malapposition immediately following stent deployment include closed-cell design, strut thickness, and acute stent recoil [21]. Besides, several mechanisms have been put forth to explain the occurrence of late acquired strut malapposition following drug-eluting stents [5] including:

- Positive arterial remodeling with an increase in total vessel area so that the vessel tends to pull away from the stent
- Dissolution of plaque and thrombus behind the stent so that a gap forms between the stent and the vessel wall, especially following primary angioplasty for acute ST-segment elevation myocardial infarction

Evidence is still pending, however, regarding the link between these findings and the risk of late and very late stent thrombosis.

Overall, coronary OCT has already come a long way since its first introduction as a late-breaking extraordinary tool for accurate, fast, and safe intravascular imaging. And, in my opinion, it has particularly proven its value over the past few years in evaluating the short- and long-term outcome of coronary stents at the level of the individual struts, so that an OCT substudy has currently become commonplace in all stent-versus-stent randomized controlled trials. Expectedly, OCT will most likely take over many of the present indications of IVUS, both as a valuable research tool, and as an indispensable clinical workhorse, alike, in cath labs worldwide.

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