Editorial

Optical coherence tomography- *vs*. intravascular ultrasound-guided percutaneous coronary intervention

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What was known before ILUMIEN 3

Coronary angiography is routinely used to guide percutaneous coronary interventions (PCI) despite obvious limitations of this lumen based approach. Intravascular imaging including intravascular ultrasound (IVUS) and optical coherence tomography (OCT) represent two techniques that provide essential information on pre-procedural lesion characteristics (i.e., lesion severity, landing zone, and plaque composition) and the result after stent implantation (i.e., stent expansion and eccentricity, strut apposition, lesion coverage, tissue protrusion, and dissections). A total of 11 randomized controlled trials investigated the effect of IVUS-guided PCI with mixed results (1-11). Of note, studies including patients with an increased complexity [i.e., chronic total occlusion (CTO) or lesion length >28 mm] demonstrated a consistent benefit of IVUS-guided PCI as compared with angiography, mainly driven by a reduction of repeat revascularization for restenosis (MACE at 1 year: CTO-IVUS, 2.6% *vs.* 7.1%, P=0.035; IVUS-XPL, 2.9% *vs.* 5.8%, P=0.007) (1,2). In addition, IVUS was instrumental in guiding left main stem PCI in the recent EXCEL and NOBLE left main trials in more than 70% of patients, although these studies were not designed to investigate effects of intracoronary-guided imaging (12,13).

OCT has a high spatial resolutions of 10–20 µm, which is approximately 10 times greater as compared with IVUS. Due to a lower tissue penetration, OCT is limited in determining the plaque burden, vessel size based on the detection of the external elastic membrane (EEM) at the minimal lumen diameter, which is one of the parameters used for IVUS-guided stent sizing (14). The majority of previous IVUS studies reportedly applied the multicenter ultrasound stenting in coronary (MUSIC) criteria (*Table 1*) (15) with the key criteria of an in-stent minimal lumen area ≥80% of the average reference lumen area or ≥90% of the lumen area of the reference segment with the lower lumen size along with symmetric stent expansion. Notwithstanding the increasing use of OCT for PCI-guidance, standard criteria for this light-based technology have not been established.

To date, the use of OCT for guiding PCI has mainly been evaluated in smaller studies, using surrogate marker endpoints (16,17). In the recent DOCTORS trial, the use of OCT-guided PCI was associated with a small but significant difference in post-procedural FFR (0.94±0.04 *vs.* 0.92±0.05, P=0.005) (18). In the OCTACS study, OCT-guidance resulted in a lower proportion of uncovered struts at 6 months (4.3% *vs.* 9.0%, P<0.01) (19).

Based on the well-established and currently still widespread clinical use of IVUS-guided PCI and the available aforementioned evidence on its effectiveness, one of the key questions is whether OCT-guided PCI using a specific protocol is comparable to IVUS-guided PCI in terms of lesion expansion. ILUMIEN 3 (20) was designed to fill this gap of clinically relevant evidence.

Table 1 Guidance criteria used in previous RCTs on IVUS- and OCT-guided PCI

Study	Year	Patient number	Stent	Criteria	No. of patients/ lesions in whom criteria were not achieved (%)
IVUS					
IVUS-XPL	2015	1,400	DES	MSA ≥ distal reference lumen area	315/678 (46.5)
CTO-IVUS	2015	402	DES	(I) MSA ≥ distal reference lumen area; (II) stent area at CTO segment ≥5 mm^2; (III) complete stent apposition	(I) 49/196 (25.0); (II) 34/196 (17.3); (III) 9/196 (4.6)
AIR-CTO	2015	230	DES	(I) Good apposition; (II) MSA >80% of reference vessel area; (III) symmetry index >0.7	10/115 (8.7)
RESET	2013	543	DES	NA	NA
AVIO	2013	284	DES	AVIO criteria (IVUS was used for optimal balloon size selection and target area evaluation)	81/156 (51.9)
HOME DES	2010	210	DES	(I) Good apposition; (II) MSA >5 mm^2 or CSA >90% of distal reference lumen CSA for small vessel	NA
AVID	2009	800	BMS	(I) The smallest CSA within the stent should be ≥90% of the distal reference vessel lumen CSA; (II) full apposition of the stent to vessel wall	223/394 (56.5)
TULIP	2003	150	BMS	(I) Complete stent apposition; (II) in-stent MLD ≥80% of the mean of proximal and distal reference diameters; (III) in-stent MLA greater than or equal to distal reference lumen area	8/73 (11.0)
OPTICUS	2001	550	BMS	MUSIC criteria: (I) complete apposition of the stent over its entire length against the vessel wall; (II) in-stent MLA ≥90% of the average reference lumen area or ≥100% of the reference segment with the lowest lumen area. In-stent lumen area of proximal stent entrance ≥90% of proximal reference lumen area; (III) symmetric stent expansion defined by minimum lumen diameter/ max lumen diameter ≥0.7	NA (43.9)
SIPS	2000	269	Provisional stenting	MUSIC criteria	52/166 (31.3)
RESIST	1998	155	BMS	Ratio of intra stent CSA to the average of the proximal and distal reference lumen CSA, with a cutoff point at 80%	16/79 (20.3)
OCT					
ILUMIEN 3	2016	450	DES	MSA of at least 90% in both the proximal and distal halves of the stent relative to the closest reference segment	82/140 (58.6)
OPINION	2017	800	DES	(I) In-stent MLA ≥90% of the average reference lumen area; (II) complete apposition of the stent; (III) symmetric stent expansion defined by minimum lumen diameter/ max lumen diameter ≥0.7; (IV) no plaque protrusion, thrombus, or edge dissection with potential to provoke flow disturbances	NA
DOCTORS	2016	250	DES or BMS	(I) In-stent MLA >80% of reference lumen area; (II) additional stent implantation(s) were to be performed to rectify incomplete lesion coverage; (III) use of GP IIb/IIIa inhibitors and aspiration thrombectomy were to be considered systematically if thrombus was present	NA
OCTACS	2015	100	DES	(I) MSA ≥90% of the distal/proximal reference vessel lumen area; (II) no significant malapposition defined as ≥3 struts per CSA detached >140 μm from the underlying vessel wall; (III) no significant edge dissection (causing minimum lumen area <4 mm^2); (IV) no significant residual stenosis (causing minimum lumen area <4 mm^2)	NA

RCT, randomized controlled trial; IVUS, intravascular ultrasound; OCT, optical coherence tomography; PCI, percutaneous coronary interventions; DES, drug eluting stent; MSA, minimum stent area; CTO, chronic total occlusion; NA, not available; CSA, cross sectional area; BMS, bare metal stent; MLD, minimum lumen diameter; MLA, minimum lumen area.

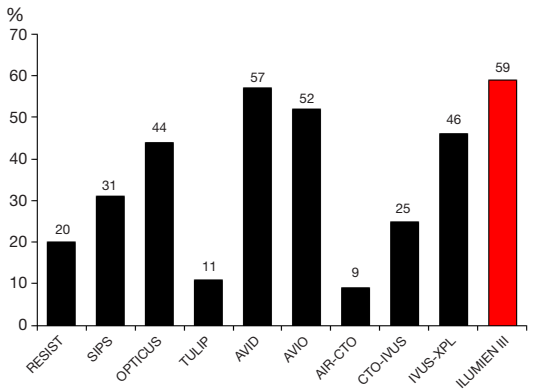

Figure 1 Percentage of patients/lesions not achieved pre-specified imaging criteria in previous randomized controlled trials.

What the study found

ILUMIEN 3 represents the first multicenter, randomized controlled trial aiming to compare the effects of OCT-guided, IVUS-guided, and angiography guided-PCI against each other (20). Relatively simple lesions [i.e., short lesion length (median length 15.5 mm), exclusion of left main, CTO and planned 2-stent bifurcation lesion, and less than 1/3 acute coronary syndrome patients] were included to this study. The primary endpoint was minimal stent area (MSA), a measure that is closely related to the risk of future stent failures. The study found that the final MSA following OCT-guided PCI [5.79 mm^2 (IQR, 4.54–7.34 mm^2)] was non-inferior to that of IVUS-guided PCI [5.89 mm^2 (IQR, 4.67–7.80 mm^2), P for non-inferiority =0.001] but not superior to that of angiography-guided PCI [5.49 mm^2 (IQR, 4.39–6.59 mm^2), P=0.12]. Conversely, minimum and mean stent expansion was significantly improved following OCT-guided PCI [87.6%±16.6% and 105.8% (IQR, 97.8–119.8%)] as compared with angiography-guided PCI [82.9%±12.9%, P=0.02 and 101.4% (IQR, 91.9–110.2%), P=0.001] and similar to that achieved by IVUS-guidance [86.5%±15.9%, P=0.77 and 106.3% (IQR, 96.7–116.6%), P=0.63]. Untreated dissections and major malapposition were significantly less frequent in OCT group [39 (28%) and 15 (11%)] compared with IVUS group [53/134 (40%), P=0.04 and 28/134 (21%), P=0.02] and angiography group [61 (44%), P=0.006 and 44 (31%), P<0.0001].

Post-dilatation represents the key corrective measures in the presence of underexpansion or stent strut malapposition and directly affects the primary endpoint of ILUMIEN 3. Post-dilatation was required to achieve a stent expansion of at least 90% in both the proximal and distal halves of the stent relative to the respective reference segment, which represents a so far unique guidance criteria introduced by ILUMIEN 3 investigators. Interestingly, the protocol-mandated expansion target was not achieved in the majority of cases (59%) and the difference in MSA was minimal as compared to the IVUS group, in which no expansion criteria was defined (IVUS 63%). There are two conceivable reasons for this observation: firstly, the expansion target >90% is too ambitious to be achieved even in simple lesions or secondly, the operators did not follow the suggested guidance protocol with sufficient adherence. The article on the study is not providing further insights in this relevant limitation of the study. As in ILUMIEN 3, several other IVUS-guided imaging studies also frequently did not achieve the protocol required expansion goal (*Figure 1*), albeit guidance-related clinical benefit reportedly emerged (i.e., XPL study). Nevertheless, expansion goals that can be achieved in daily routine appear relevant and insights obtained in ILUMIEN 3 should further assist in determining those.

Regarding the operators' adherence to the imaging protocol, the higher number of post-dilation performed in the imaging groups (2 *vs.* 1) and the larger balloons indicate that, the information obtained by imaging was applied at least in part and translated into additional attempts to expand the stent better. Whether a more aggressive approach could have led to a more meaningful difference in stent expansion without compromising safety remains unknown.

Regarding the use of IVUS, no dedicated guidance protocol was available leaving the decision, how IVUS should be used to select stent size and optimize the results at the discretion of the operator. This potentially puts IVUS at disadvantage, at least regarding the primary endpoint measure.

The ILUMIEN 3 study also provides insights into secondary endpoints that were previously associated with adverse events.

Dissections

The frequency of any dissection at the end of the procedure was significantly lower in the OCT (28%) as compared to IVUS (40%, P=0.04) and angiography group (44%, P=0.006). When only considering major dissections (i.e., those with potential clinical impact), the difference between OCT and angiography disappeared, while IVUS was associated with a persisting increased risk. The use of OCT could only lead to fewer dissections by a more frequent identification and subsequent treatment of these tears by additional stent implantation, something that is not

mentioned in the article. In the absence of such evidence, the difference is likely explained by chance or alternatively, the use of IVUS could be associated with an increased risk of causing dissections.

Malapposition

Untreated major stent malapposition after PCI was less frequent in the OCT group (11%) as compared with the IVUS (21%, P=0.02) and angiography group (31%, P<0.0001). The findings of malapposed struts are clinically relevant: previous studies consistently reported that malapposition after PCI was the leading cause underlying early and very late stent thrombosis (21,22). In the ILUMIEN 3 trial, major malapposition was defined as ≥200 µm and associated with a stent underexpansion <90%. A previous study reported that struts with an axial malapposition distance of <270 µm will heal spontaneously in 100% of cases (23), suggesting that the axial cutoff for major malapposition may be sensitive. Also, in a previous OCT study in very late stent thrombosis patients, the malapposition length rather than the axial distance emerged as the most relevant correlate of thrombus formation (22). How results between groups would differ when considering a less aggressive threshold for the axial distance (e.g., >300 µm) and when also including the longitudinal extension (e.g., >1 mm) remains open to question.

Stent sizing based on EEM tracing

This study proposed a new stent sizing protocol based on the delineation of the distance between the EEM at the reference vessel segment mainly to overcome the issue encountered in the ILUMIEN 1 study where OCT (as compared to angiography) led the operators select smaller stents (24). The identification of the EEM by OCT may be challenging and time consuming considering that even in the hands of highly trained intracoronary imaging experts, EEM tracing is not possible in one fourth of cases, although similar average stent diameter in the IVUS and OCT group reassuringly confirms that the novel OCT sizing algorithm is resulting in similar stent dimensions. As a simple approach to PCI guidance is a key for the uptake by a broader interventional community, it should be investigated within the ILUMIEN 3 trial data whether a simplified approach considering the mean lumen reference diameter and a standardized upgrading of the stent size could lead to a comparable stent size selection.

Other recent trials with similar focus

Differences in clinical outcomes were not observed. Recently, the results of the OPINION study, a multicenter, prospective, randomized trial testing whether OCT-guided PCI is non-inferior compared with IVUS-guided PCI with respect to the clinical endpoint target vessel failure was presented (25). Indeed, the primary endpoint occurred in a similar frequency between groups (5.2% *vs.* 4.9%, P for non-inferiority <0.05) confirming non-inferiority of OCT compared with IVUS. In addition, in-stent minimum lumen diameter as assessed by quantitative coronary angiography at 8 months was identical (2.38±0.51 *vs.* 2.44±0.52 mm, P=0.136). In variance to the ILUMIEN 3, the OPINION study did not include an angiography-guided control arm. Notwithstanding this limitation, the ILUMIEN and OPINION studies consistently provide reassurance that OCT is at least equal to IVUS for PCI guidance, supporting the current shift from IVUS to OCT in most cath labs by important evidence. Although IVUS-guidance has shown to result in improved outcomes in a complex PCI setting, a dedicated outcome study is required with the use of OCT. When designing such a study, lessons learnt should be considered by designing a study that is adequately powered and by considering only patients that indeed are anticipated to benefit from intracoronary imaging guidance, i.e., those with an increased level of complexity on patient (e.g., diabetes mellitus) and lesion level (e.g., long lesions, CTO, left main, and bifurcations). Another challenging task is to define meaningful thresholds based on a distillation of previous studies that investigated stent failures. Thresholds that set the bar for intervention too low ultimately result in overtreatment whereas too high thresholds for corrective measures will leave behind findings that may trigger future cardiovascular events. Finally, simplified criteria represent a key determinant to bring OCT guidance to a success for routine clinical practice in complex PCI.

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Footnote

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