

OCT-Guided PCI: Lessons From the ILUMIEN IV: OPTIMAL PCI Trial

A discussion of study design, insights into the results, and the current and future role of OCT-guided stent implantation and optimization.

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Intravascular imaging has important benefits over angiography during percutaneous coronary interventions (PCI) in (1) determining plaque characteristics and reference vessel size prior to stent implantation and (2) identifying stent underexpansion, malapposition, edge dissection, and residual disease in the reference vessel segments after PCI. Several randomized trials and meta-analyses have shown that intravascular ultrasound (IVUS)-guided PCI can improve clinical outcomes.¹⁻⁴ Optical coherence tomography (OCT) is a newer intravascular imaging modality with higher resolution compared with IVUS. In the ILUMIEN III: OPTIMIZE PCI trial, OCT-guided PCI was found to be noninferior to IVUS- or angiography-guided PCI with respect to post-PCI minimum stent area (MSA) and was superior to angiography-guided PCI in achieving larger stent expansion in noncomplex coronary lesions, with the least number of untreated procedural complications.⁵ The ILUMIEN IV: OPTIMAL PCI trial was performed to determine whether these improvements in procedural outcomes could translate into improvements in clinical outcomes, particularly in high-risk patients and lesions most likely to benefit from OCT-guided PCI. This article reviews the study design and results of ILUMIEN IV and its clinical implications.^{6,7}

STUDY DESIGN SUMMARY OF ILUMIEN IV: OPTIMAL PCI

The ILUMIEN IV was a global, prospective, single-blind, randomized trial investigating OCT-guided PCI versus angiography-guided PCI.^{6,7} The objective of the trial was to demonstrate the superiority of OCT-

guided PCI in achieving greater lumen dimensions after stent implantation and improving clinical outcomes in high-risk patients and lesions.⁶ High-risk patients were defined as those with medication-treated diabetes. High-risk lesions included target lesions responsible for acute coronary syndrome (ACS), long or multiple lesions requiring a total stent length ≥ 28 mm, a bifurcation lesion with two planned stents, angiographic severe calcification, chronic total occlusion, or in-stent restenosis.⁶ There were two separately powered primary endpoints: The imaging coprimary endpoint was final post-PCI MSA, and the clinical coprimary endpoint was target vessel failure (TVF) within 2 years, defined as the composite of cardiac death, target vessel-related myocardial infarction (MI), or ischemia-driven target vessel revascularization (TVR) (see Sidebar).⁶

OCT-Guided PCI Protocol in ILUMIEN IV: OPTIMAL PCI

In the OCT-guided arm, patients underwent treatment according to a specific algorithm, similar to the MLD MAX algorithm previously described by us (Figures 1 and 2).⁸ In pre-PCI OCT imaging, the morphology was assessed to determine lesion preparation; the proximal and distal reference segments were identified, and the stent length was determined by the distance between the two segments. To determine the stent size, the external elastic lamina (EEL)-based mean diameter of the distal reference was rounded down to the nearest available stent size. If the EEL could not be adequately visualized, the mean lumen diameter of the distal reference was rounded up to the next available stent size. After stent implantation, optimization was performed with non-

ILUMIEN IV: OPTIMAL PCI STUDY DESIGN SUMMARY



OBJECTIVE

To demonstrate the superiority of OCT-guided PCI in achieving greater lumen dimensions after stent implantation and improving clinical outcomes in high-risk patients and lesions



STUDY DESIGN

Global, prospective, single-blind, randomized trial



PATIENT POPULATION

2,487 total patients were randomized

- OCT-guided PCI (n = 1,233)
- Angiography-guided PCI (n = 1,254)



DEFINITIONS

High-risk patients: Those with medication-treated diabetes

High-risk lesions: Target lesions responsible for ACS, long or multiple lesions requiring a total stent length ≥ 28 mm, a bifurcation lesion with two planned stents, angiographic severe calcification, chronic total occlusion, or in-stent restenosis

TVF: Composite of cardiac death, target vessel-related MI, or ischemia-driven TVR



PRIMARY ENDPOINTS

- Final post-PCI MSA
- TVF within 2 years

compliant balloons based on the respective reference diameter measurements. Post-PCI OCT imaging was then repeated and, if needed, iterative postdilation was performed in an attempt to achieve acceptable stent expansion with MSA $\geq 90\%$ relative to the closest reference segments. If there was untreated inflow/outflow disease, defined as a minimal lumen area < 4.5 mm² within 5 mm from the edges of the stent, or a major edge dissection, defined as dissection involving $\geq 60^\circ$ of the circumference of the vessel and ≥ 3 mm in length, additional stent implantation was performed unless anatomically prohibitive (eg, biological vessel tapering, distal diffuse disease, absence of landing zone). After optimization, final OCT imaging was performed. In the angiography arm, PCI was performed as per standard of care, with a final blinded OCT to capture the imaging endpoints.

Results of the ILUMIEN IV: OPTIMAL PCI Trial

From May 17, 2018, through December 29, 2020, a total of 2,487 patients were randomly assigned to undergo OCT-guided PCI (n = 1,233) or angiography-guided PCI (n = 1,254) at 80 sites in 18 countries.⁷ Baseline char-

acteristics were comparable between the two groups, and 40.1% were high-risk patients with medication-treated diabetes. The most common qualifying lesion characteristics were long or multiple lesions requiring a total stent length ≥ 28 mm (67.6%), followed by ACS (29.6%) and angiographic severe calcification (11.5%). Compared with angiographic guidance, OCT guidance led to longer and larger stents, larger maximum balloon size, and more frequent postdilation with higher pressure. Procedure times, fluoroscopy duration, radiation dose, and contrast volume were higher with OCT guidance.

For the imaging primary endpoint, OCT-guided PCI led to a significantly larger final MSA (5.72 ± 2.04 mm² vs 5.36 ± 1.87 mm²; difference, 0.36 mm²; 95% CI, 0.21-0.51; $P < .001$). OCT guidance also resulted in a greater stent expansion than angiographic guidance (minimal stent expansion: $80.8\% \pm 16.8\%$ vs $77.9\% \pm 16.7\%$, respectively; difference, 2.9% [95% CI, 1.6%-4.2%]; mean stent expansion: $111.3\% \pm 16.3\%$ vs $103.0\% \pm 17.2\%$; difference, 8.2% [95% CI, 6.9%-9.5%]). OCT-assessed procedural complications were also lower in the OCT-guided arm. Major dissections, malapposition, tissue protrusion, and

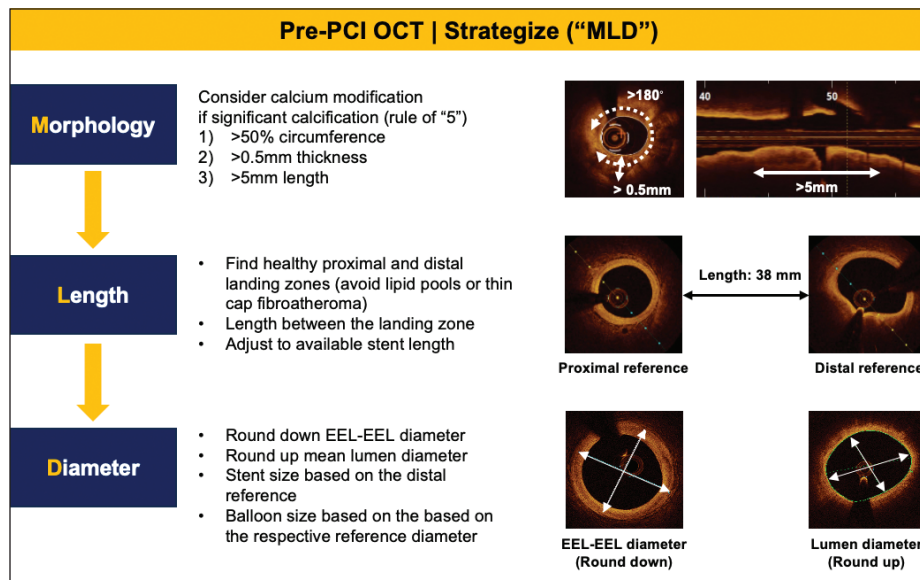


Figure 1. OCT-guided pre-PCI strategy by the MLD-MAX algorithm. Components and examples of pre-PCI strategization of the MLD-MAX algorithm (“MLD”) are presented.

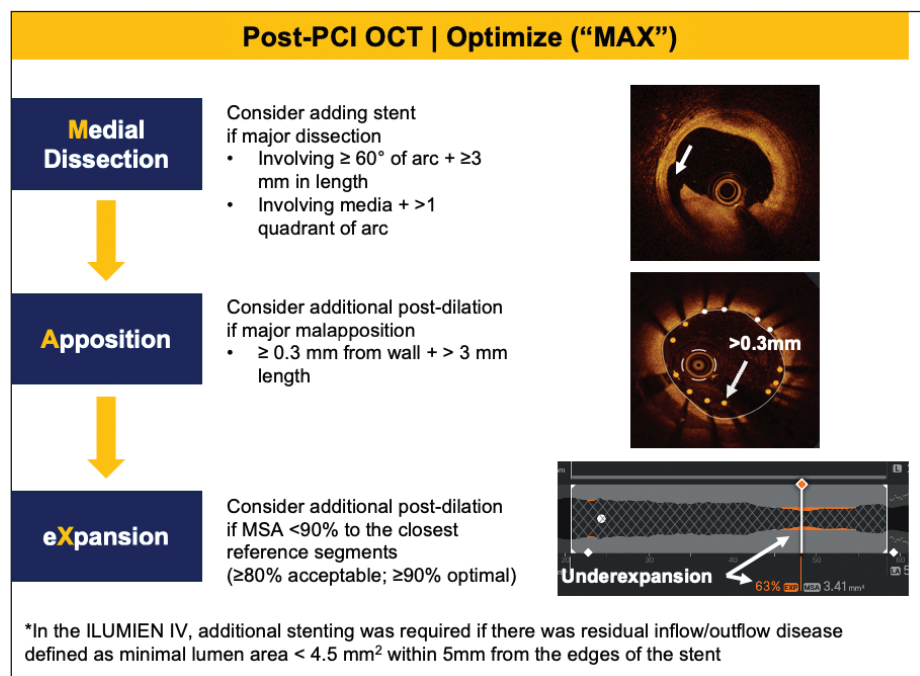


Figure 2. OCT-guided post-PCI optimization by MLD-MAX algorithm. Components and examples of post-PCI optimization of the MLD-MAX algorithm (“MAX”) are presented.

untreated focal reference segment disease were all lower in the OCT-guided versus the angiographic-guided arm.

The clinical primary endpoint, TVF within 2 years, occurred less in the OCT guidance group than in the angiography guidance group (7.4% vs 8.2%, respectively), but this difference was not statistically significant (haz-

ard ratio [HR], 0.90; 95% CI, 0.67-1.19; $P = .25$). In terms of individual components of the clinical primary endpoint, cardiac death (0.8% vs 1.3%; HR, 0.57; 95% CI, 0.25-1.29) and target vessel-related MI (2.5% vs 3.3%; HR, 0.77; 95% CI, 0.48-1.22) occurred less in the OCT guidance group, but these differences were not statistically significant. Event rates for ischemia-driven TVR were the same in both groups (5.6% vs 5.6%; HR, 0.99; 95% CI, 0.71-1.40).

Among the safety secondary outcomes, OCT-guided PCI resulted in 64% less definite or probable stent thrombosis than angiography-guided PCI (0.5% vs 1.4%, respectively; HR, 0.36; 95% CI, 0.14-0.91; $P = .02$). OCT-related complications were very rare in both groups (0.1%-0.2%), and angiographic complications were lower in the OCT-guided arm, driven by a reduction in intraprocedural thrombotic events.

DISCUSSION POINTS

ILUMIEN IV confirmed a number of benefits to OCT-guided PCI compared with angiography-guided PCI. First, OCT-guided PCI led to a greater post-PCI MSA, which has consistently been shown to be one of the strongest stent-related parameters to predict clinical outcomes.^{5,9-14} In

its predecessor, ILUMIEN III, the final median MSA was 5.79 mm² (IQR, 4.54-7.34 mm²) with OCT guidance and 5.49 mm² (IQR, 4.39-6.59 mm²) with angiography guidance, but it was not statistically significant due to limited sample size.⁵ This 0.30-mm² difference in the final MSA favoring OCT-guided PCI was replicated and

confirmed in ILUMIEN IV, where the difference was 0.36 mm^2 (95% CI, $0.21\text{--}0.51 \text{ mm}^2$) and statistically significant ($P < .001$).⁷ The improvement in the final MSA was due to more frequent advanced lesion preparation, larger stents, larger maximum balloon size, and more frequent postdilation with higher pressures in the OCT guidance group. Second, OCT-guided PCI significantly improved safety outcomes with fewer acute procedural complications and less stent thrombosis. OCT-guided PCI was associated with a 64% reduction in the risk of definite or probable stent thrombosis compared with angiography-guided PCI—the most devastating stent-specific complication of PCI.¹⁵ It is important to note that 96% of patients with stent thrombosis in the ILUMIEN IV died or had an MI within 2 years. This reduction in stent thrombosis and procedural complications can be tied to the reduction in OCT-guided PCI leading to less major edge dissection, major malapposition, major tissue protrusion, and untreated focal reference segment disease compared with angiography-guided PCI, all of which have previously been associated with fewer adverse events.^{14,16,17}

Despite the procedural and safety benefits described previously, the ILUMIEN IV trial was neutral with respect to improvement in the primary clinical endpoint: TVF within 2 years. This result was largely due to equipoise in ischemia-driven TVR between the two groups (5.6% vs 5.6%; HR, 0.99; 95% CI, $0.71\text{--}1.39$; $P = .97$). Because the majority of events in the TVF composite come from ischemia-driven TVR, this equipoise drove the neutral findings. The event rates of ischemia-driven TVR, especially after angiography-guided PCI, were much lower than expected considering the high-risk patients and lesions enrolled in the trial. There are two predominant explanations. First, COVID-19 might have impacted the low rates of ischemia-driven TVR. The ILUMIEN IV trial enrolled and followed patients during the COVID-19 pandemic, when many patients had significantly limited access to the health care system or opted not to seek immediate medical attention due to apprehension of contracting the virus. Therefore, those with progressive angina were more likely to be managed medically, which could have potentially biased the findings toward the mean. In fact, among the patients enrolled prior to the COVID-19 pandemic with at least 1 year of follow-up, TVF occurred in 7.2% in the OCT guidance group and 10.1% in the angiography guidance group (HR, 0.70; 95% CI, $0.37\text{--}1.32$), which was consistent with the original hypothesis of the trial.¹⁸ It would be interesting to see whether there is a late catch-up phenomenon with a longer follow-up. Second, some of the high enrollers

of the trial routinely use intravascular imaging in their daily practice. Those operators are likely to have lessons learned from their imaging experience applied to angiography-guided PCI even without intravascular imaging guidance.

INTRAVASCULAR IMAGING–GUIDED PCI: WHERE ARE WE NOW?

Recently, several randomized trials have consistently demonstrated the benefits of intravascular imaging–guided PCI over imaging–guided PCI.^{19,20} ILUMIEN IV is by far the largest and the first global randomized trial comparing intravascular imaging–guided PCI with angiography-guided PCI, and the results should be interpreted in the context of all other trials. The most updated network meta-analysis of 20 randomized trials with 12,428 patients, including ILUMIEN IV, found that intravascular imaging–guided PCI (either IVUS or OCT) was associated with significantly lower risks of almost all clinical outcomes, such as TVF (relative risk [RR], 0.69; 95% CI, $0.40\text{--}0.74$), cardiac death (RR, 0.54; 95% CI, $0.40\text{--}0.74$), all-cause death (RR, 0.75; 95% CI, $0.60\text{--}0.93$), target vessel–related MI (RR, 0.80; 95% CI, $0.66\text{--}0.97$), any MI (RR, 0.82; 95% CI, $0.69\text{--}0.98$), stent thrombosis (RR, 0.48; 95% CI, $0.31\text{--}0.76$), and target lesion revascularization (RR, 0.71; 95% CI, $0.59\text{--}0.85$).²¹ Based on the network comparison, outcomes were similar between OCT- and IVUS-guided PCI,²¹ which was also confirmed in a recent large-scale randomized trial.²²

In reality, the overall adoption rate of intravascular imaging remains at $< 15\%$ of all PCI procedures in the United States.²³ Because evidence supporting the benefits of intravascular imaging–guided PCI has only become more robust, now is the time to consider changing our guidelines and recommending intravascular imaging–guided PCI as class Ia, especially in high-risk patients and lesions. This should be followed by concentrated education and training and sufficient reimbursement, which are critical to overcome two predominant obstacles: fear and finance.²⁴

CONCLUSION

The ILUMIEN IV: OPTIMIZE PCI trial illuminated the beneficial role of OCT-guided stent implantation and optimization, which increased procedural success and safety and reduced stent-related complications. Although there was no apparent difference in TVF within 2 years, the results of the pooled analysis of numerous trials, including ILUMIEN IV, clearly favored intravascular imaging–guided PCI over angiography-guided PCI. With the overwhelming burden of evidence, it would be better late than never to move forward. ■

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Disclosures: Institutional grants from Abbott, Abiomed, Acist Medical, Boston Scientific, Cardiovascular Systems, Inc., Medtronic, OpSens Medical, Philips, and Shockwave Medical; personal fees from Amgen, AstraZeneca, and Boston Scientific; equity from Elucid, LifeLink, Spectrawave, Shockwave Medical, and Vital Connect.

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