Journal of the Society for Cardiovascular Angiography & Interventions 2 (2023) 101118

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

ISR vs De Novo Lesion Treatment During OCT-Guided PCI: Insights From the LightLab Initiative

Brian A. Bergmark, MD [a,b], Mordechai Golomb, MD [c], Julia F. Kuder, MA [b], Jana Buccola, MS [d], Jason Wollmuth, MD [e], John Lopez, MD [f], Judah Rauch, MD [g], Bassem M. Chehab, MD [h], Richard Rapoza, PhD [d], Nick E.J. West, MD [d], Kevin J. Croce, MD, PhD [a,*]

[a] *CTO/Complex Coronary Intervention Program, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts;* [b] *Thrombolysis in Myocardial Infarction (TIMI) Study Group, Boston, Massachusetts;* [c] *Hadassah Hebrew University Medical Center, Tel Aviv, Israel;* [d] *Abbott Vascular, Santa Clara, California;* [e] *Providence St. Vincent Hospital, Portland, Oregon;* [f] *Loyola University Medical Center, Maywood, Illinois;* [g] *Albert Einstein College of Medicine, New York, New York;* [h] *Ascension Via Christi Hospital, University of Kansas, Wichita, Kansas*

ABSTRACT

Background: Long-term outcomes after percutaneous coronary intervention (PCI) for in-stent restenosis (ISR) are poor, yet limited granular procedural data exist evaluating lesion assessment, vessel treatment, and acute procedural outcomes.

Methods: The LightLab Initiative was a multicenter, prospective, observational study with contemporaneous procedural data collection during PCI procedures. Data were collected during PCIs performed by 48 interventional cardiologists at 17 US hospitals (2019-2021). Optical coherence tomography (OCT) was performed pre-PCI for lesion assessment and post-PCI for stent optimization, and results were compared between ISR and de novo lesion PCI.

Results: In total, 2592 OCT-guided PCIs involving 2944 lesions were included, of which 458 procedures (17.7%) were ISR PCI. Compared with de novo lesion PCI, ISR lesions were more commonly type C (64.8% vs 52.9%) and performed via femoral artery access (46.4% vs 37.7%). Use of OCT changed operator assessment and treatment decisions more frequently in ISR PCI (94.2% vs 85.2%; $P = .002$). Scoring balloons (21.8% vs 2.5%), cutting balloons (16.4% vs 3.4%), and atherectomy (26.3% vs 9.9%) were used more commonly in ISR PCI (all $P < .0001$), and ISR PCI procedures were longer (62 vs 51 min). Moreover, the final achieved minimum stent area and percent expansion (4.4 vs 5.1 mm^2 and 80% vs 83%, respectively; both $P < .0001$) were lower in ISR PCI.

Conclusions: In this real-world cohort of patients who underwent OCT-guided PCI, ISR procedures were longer and final minimum stent area and percent expansion were lower despite greater use of advanced lesion modification. OCT frequently altered physician decision making, emphasizing its utility in potentially reducing recurrent stent failure in this high-risk population.

Introduction

Despite improvements in coronary stent design and percutaneous coronary intervention (PCI) technique, stent failure due to in-stent restenosis (ISR) remains a persistent challenge.[1–3] Intervention for ISR accounts for approximately 10% of PCIs performed in the United States annually,[1,2] but this number may underrepresent the true magnitude of the problem because many patients with ISR may be treated medically or with bypass surgery. In fact, among patients with established atherosclerosis who underwent revascularization in the course of the FOURIER trial, 27% had ISR identified at the time of coronary revascularization.[4]

Further, ISR PCI is associated with poor long-term outcomes compared with PCI for de novo coronary lesions.[2,3] Although intracoronary imaging can potentially improve PCI outcomes, as has most recently been demonstrated by the RENOVATE-COMPLEX-PCI trial[5] of intracoronary imaging vs angio-guided PCI in complex coronary lesions, current guidelines only afford a IIa/B recommendation for use in PCI procedures to optimize stent results and IIa/C for use in ISR PCI.[6,7] One of the current gaps in evidence is that limited granular procedural data exist for ISR vs de novo lesion PCI, particularly with regard to impact and results of intracoronary imaging.

We therefore sought to evaluate ISR vs de novo lesion PCI using data from the LightLab Initiative, a prospective multicenter study of real-world PCI guided by optical coherence tomography (OCT).[8–10]

Abbreviations: ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Keywords: in-stent restenosis; intravascular imaging; optical coherence tomography; percutaneous coronary intervention.

* Corresponding author: kcroce@bwh.harvard.edu (K.J. Croce).

https://doi.org/10.1016/j.jscai.2023.101118
Received 15 May 2023; Received in revised form 13 July 2023; Accepted 21 July 2023
Available online 12 August 2023

Methods

Study overview

The LightLab Initiative (LightLab) was a prospective, observational study performed at 17 US hospitals with data collected during procedures performed by 48 interventional cardiologists from 2019 to 2021. Physicians performed pre-PCI and post-PCI OCT according to a standardized workflow referred to as MLD MAX (morphology, length, diameter, medial dissection, apposition, and expansion).[8,9,11,12] LightLab was designed in collaboration with Abbott, the sponsor of the study, and academic partners. The study database was separately held at Abbott and the Thrombolysis in Myocardial Infarction (TIMI) Study Group at the Brigham and Women's Hospital.

Data collection and procedures

Intraprocedural data were collected contemporaneously by field clinical engineers using a tablet-based data collection form (Vablet). Physician assessment of the lesion(s) and PCI treatment plan were recorded after the pre-PCI and post-PCI angiograms and after the pre-PCI and post-PCI OCT runs. Variables collected pre-OCT and post-OCT have been described previously.[8,9] For the analyses reported in this study, only procedures with ISR or de novo lesion PCI with pre-PCI and post-PCI OCT were included. The MLD MAX workflow[12] followed in LightLab utilized the ILUMIEN OPTIS, OPTIS Integrated, and OPTIS Mobile systems with Dragonfly OPTIS and OpStar OCT catheters in accordance with their approved indications (Abbott).

Statistical analysis

Procedures were classified as having OCT-guided PCI to at least 1 lesion or no OCT-guided PCI. Procedures with OCT-guided PCI were then further classified as having PCI to at least 1 ISR lesion or to all de novo lesions. Lesion-level PCI description was then based on whether each specific lesion was ISR or de novo. Percent expansion was calculated by comparing the proximal half of the stented segment to the proximal reference and the distal half of the stented segment to the distal reference. Proportions are presented as n/N and percentages, with comparisons made between groups using the χ^2 test. Continuous variables were compared using the Wilcoxon rank sum test. All analyses were performed by the TIMI Study Group using SAS version 9.4 (SAS Institute). A P value of $<.05$ was considered significant for all comparisons with no adjustment for multiple testing. The study database cannot be shared, but those interested in academic collaboration can contact the corresponding author.

Results

Data were collected from 9759 procedures from January 2019 to June 2021 (Figure 1). Of these, 2638 procedures involved OCT-guided PCI to treat at least 1 lesion. After exclusion of 46 procedures, largely for concomitant mechanical circulatory support use, 2592 OCT-guided PCI procedures involving 2,944 lesions were included. Intervention on at least 1 ISR lesion was performed in 458 (17.7%) procedures, and 2134 (82.3%) PCIs involved only de novo lesions. Among the procedures involving PCI to at least 1 ISR lesion, there were a total of 463 ISR lesions treated with OCT-guided PCI. The total number of de novo lesions treated with OCT-guided PCI was 2481.

Procedural and lesion characteristics are provided in Table 1. Procedures involving ISR PCI were more likely to involve femoral arterial access (46.4% vs 37.7%; $P = .03$) and multivessel disease including a graft (1.5% vs 0.4%; $P = .019$) than de novo PCI procedures and were less likely to be performed in the setting of STEMI (2.8% vs 5.9%; $P = .005$). The target vessel distribution varied significantly on a lesion-level basis, with ISR PCI more likely to involve the right coronary artery (33.1% vs 27.8%) and bypass grafts (2.4% vs 1.3%), and de novo PCI occurring more commonly in the left anterior descending artery (48.6% vs 41.6%).

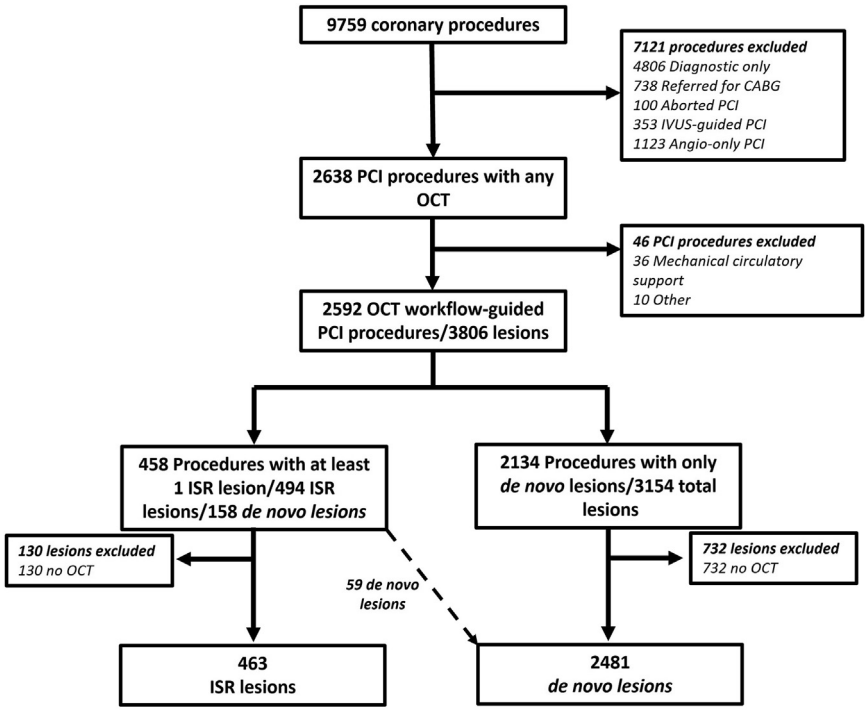


Figure 1.
Study flowchart for ISR vs de novo PCI procedures and lesions. CABG, coronary artery bypass graft surgery; ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Table 1. Baseline procedural and lesion characteristics.

Procedural characteristics	Procedures with ≥1 ISR lesion PCI (n = 458)	Procedures with only de novo lesion PCI (n = 2134)	*P*
Elective	160 (35.0)	716 (33.6)	.568
STEMI	13 (2.8)	125 (5.9)	.005
No. of lesions treated			.369
1	353 (77.1)	1591 (74.6)	
2	90 (19.7)	445 (20.9)	
>2	15 (3.3)	96 (4.5)	
Disease distribution			.019
Single vessel, 1 lesion	353 (77.1)	1591 (74.6)	
Single vessel, >1 lesion	52 (11.4)	255 (12.0)	
Multivessel disease	46 (10.0)	278 (13.0)	
Multiple lesions, ≥1 in graft	7 (1.5)	8 (0.4)	
Access site			.003
Radial	230 (52.3)	1269 (61.2)	
Femoral	204 (46.4)	781 (37.7)	
Radial and femoral	6 (1.4)	22 (1.1)	
Lesion characteristics	**ISR lesion PCI (n = 463)**	**De novo lesion PCI (n = 2481)**	
Lesion location			.028
Left main	9 (2.0)	43 (1.8)	
Left anterior descending artery	187 (41.6)	1212 (49.6)	
Left circumflex	87 (19.3)	439 (18.0)	
Ramus	7 (1.6)	41 (1.7)	
Right coronary artery	149 (33.1)	679 (27.8)	
Graft	11 (2.4)	31 (1.3)	
Lesion type			<.0001
A	13 (2.9)	195 (8.2)	
B	147 (32.3)	922 (38.9)	
C	295 (64.8)	1256 (52.9)	
Long lesion (>28.0 mm by OCT)	227 (52.1)	1035 (47.7)	.098
Chronic total occlusion	28 (6.3)	106 (4.9)	.216
Bifurcation	22 (5.0)	275 (12.7)	<.0001
Ostial lesion	13 (2.9)	99 (4.2)	.197
Proximal reference diameter[a], mm	3.60 (3.23-4.23)	3.76 (3.36-4.02)	.041
Distal reference diameter[a], mm	3.20 (2.80-3.68)	3.21 (2.75-3.55)	.907
Lesion length by OCT, mm	28 (17.5-36.0)	26 (18.0-38.0)	.031

Data are provided as n (%) or median (IQR).
ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a] As determined by external elastic lamina measurement.

A greater proportion of ISR PCIs were type C lesions (64.8% vs 52.9%; $P < .0001$), and fewer were bifurcation PCIs (5.0% vs 12.7%; $P < .0001$) than those of de novo PCIs. These findings were similar when patients with both ISR and de novo lesion PCI were removed (Supplemental Table S1).

Impact of OCT on procedural decision making in ISR vs de novo lesion PCI

Overall, OCT impacted operator intraprocedural decision making in 94.2% of ISR PCIs and 85.2% of non-ISR PCIs ($P = .002$) (Figure 2). This difference was driven by a greater degree of impact from the pre-PCI OCT (ISR: 89.9% vs de novo: 78.8%; $P = .001$) that that from the post-PCI OCT (ISR: 34.8% vs de novo: 29.9%; $P = .250$). The impact of OCT on decision making was greater overall in ISR PCI than that in de novo PCI for lesion morphology, vessel preparation plan, and treatment strategy ($P < .05$ for all).

In 51.5% of ISR PCIs, the pre-PCI OCT changed the operator's assessment of the mechanism of stent failure (Figure 3). In the majority of these cases (76.1%), the operator had identified a cause of stent failure based on the angiogram but changed this assessment based on the OCT imaging. In 23.9% of cases, the operator had not identified ISR as being present from the angiogram or had not identified a mechanism.

Device utilization and procedural success

Interventions for ISR had more frequent use of scoring balloons (21.8% vs 2.5%; $P < .0001$), cutting balloons (16.4% vs 3.4%; $P < .0001$), and atherectomy (26.3% vs 9.9%; $P < .0001$) than de novo lesion PCI (Figure 4 and Central Illustration). ISR PCI procedures were overall longer, with a median time of 61.7 minutes (IQR, 45-90 minutes) compared with a median of 50.7 minutes (IQR, 38-71 minutes) for de novo lesion PCI ($P < .0001$). The difference in procedure duration was driven by longer time for diagnosis (12.1 [IQR, 9-18] vs 10.4 [IQR, 8-15] minutes; $P < .0001$) and time for vessel preparation (8.0 [IQR, 2-19] vs 2.5 [IQR, 1-7] minutes; $P < .0001$).

The median minimum stent area (MSA) increased in ISR lesions from 2.3 mm^2 (IQR, 1.5-3.6) pre-PCI to 4.4 mm^2 (IQR, 3.3-5.9) post-PCI ($P < 0.0001$), but this final MSA for ISR lesions was lower than that for de novo lesions (5.1 mm^2 [IQR, 3.9-6.6]; $P < .0001$). The achieved percent expansion was also lower for ISR lesions (80.0% [IQR, 68.2-88.0]) than that for de novo lesions (83.0% [IQR, 73.0-92.0]; $P < .0001$) (Central Illustration).

Discussion

This analysis of OCT-guided PCI in a real-world study of 2944 lesions showed 3 principal findings: (1) ISR PCI was common, occurring in 18% of PCI procedures; (2) OCT changed the operator's assessment in 94% of ISR PCIs and 85% of de novo lesion PCIs; and (3) despite longer procedures with higher rates of scoring balloon, cutting balloon, and atherectomy use, final MSA and percent expansion were lower in ISR PCI than those in de novo lesion PCI.

With respect to the first finding, this analysis emphasizes that ISR remains a common issue. The most recent comprehensive nationwide

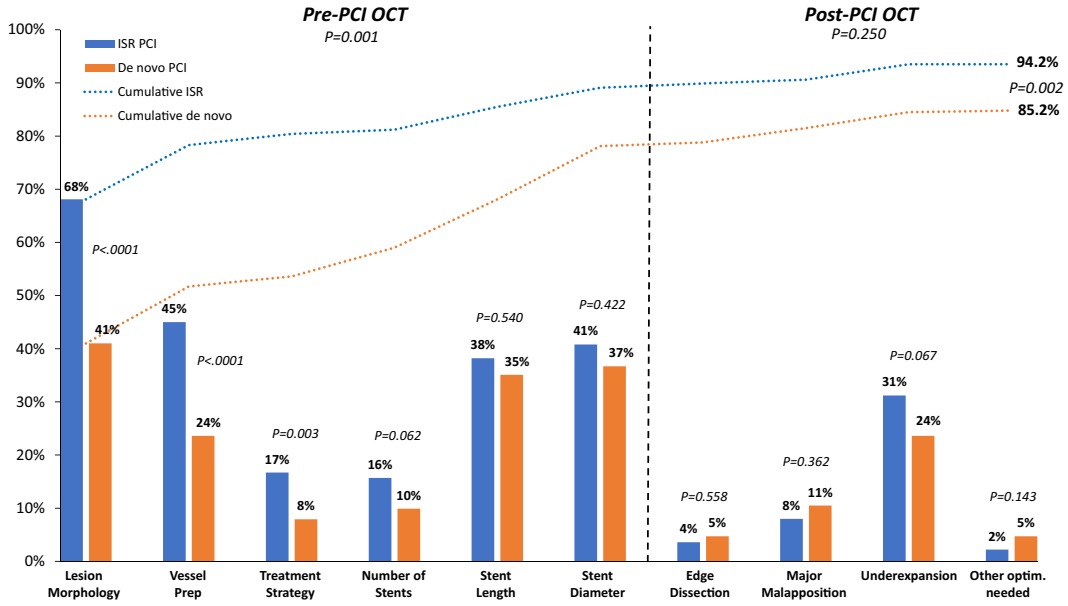


Figure 2.
Impact of OCT on decision making for ISR vs de novo PCI. CABG, coronary artery bypass graft surgery; ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

data for the United States are now several years old,[1,2] and the observation that 18% of PCIs in this relatively unselected population were for ISR suggests that rates of ISR are not declining from the previously reported ~10% of PCIs. Almost certainly, the high frequency of ISR PCI is at least in part due to low adoption of intracoronary imaging and physiology use in index de novo PCI procedures in the United States.[13,14] With randomized trial data showing improved clinical outcomes and halving of stent failure with prescriptive intracoronary imaging use during PCI[5,15–17] as well as observational data showing a significant portion of patients having residual flow-limiting disease immediately after visually successful PCI,[14] these findings reinforce the importance of performing optimized, state-of-the-art PCI in all patients during the index PCI.

Second, intracoronary imaging with OCT changed the operator's assessment in the vast majority of lesions, with a greater impact in ISR PCI than that in de novo lesions. This impact included a change in vessel preparation strategy in nearly half of ISR PCIs, as well as a change in overall treatment strategy, for example, to place a stent or treat with angioplasty only, in 17%. This observation is likely related to the finding that OCT changed the operator's assessment of the mechanism of ISR in just over half of cases, with no ISR having been identified in nearly one-quarter of these. Not surprisingly, once a treatment strategy had been identified and executed, there was a lesser degree of differential impact between ISR and de novo PCI with the post-PCI OCT. As such, performing only post-PCI OCT may fail to capture the full potential benefit of intracoronary imaging, particularly when treating ISR.

Finally, these granular procedural data may provide some mechanistic insights into the known association between ISR PCI and poor long-term clinical outcomes relative to de novo lesion PCI.[2,3,18] Scoring balloons, cutting balloons, and laser, rotational, and orbital atherectomy have proposed rationales in ISR PCI with the goal of increasing luminal gain.[18,19] Here, we found that these devices were used at higher rates in ISR PCI, including a nearly 3-fold higher rate of atherectomy use. Nonetheless, the MSA at procedure completion was lower for ISR PCI, as

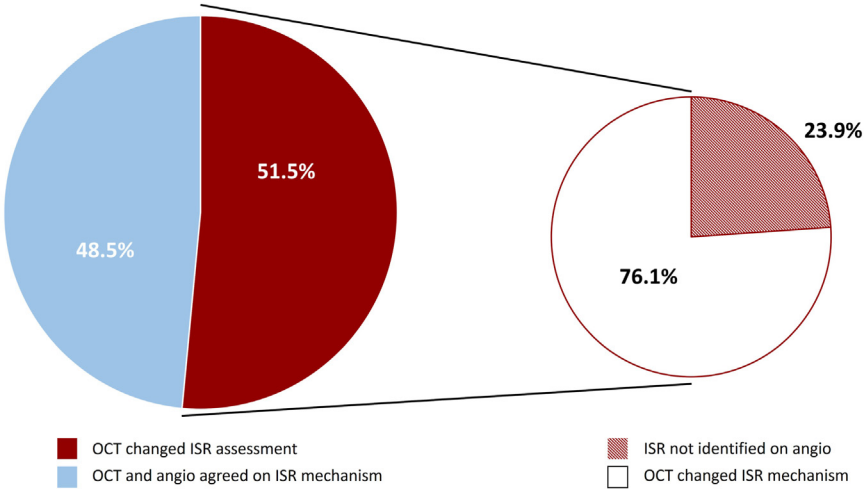


Figure 3.
Change in ISR assessment with OCT compared with that in angiography. CABG, coronary artery bypass graft surgery; ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

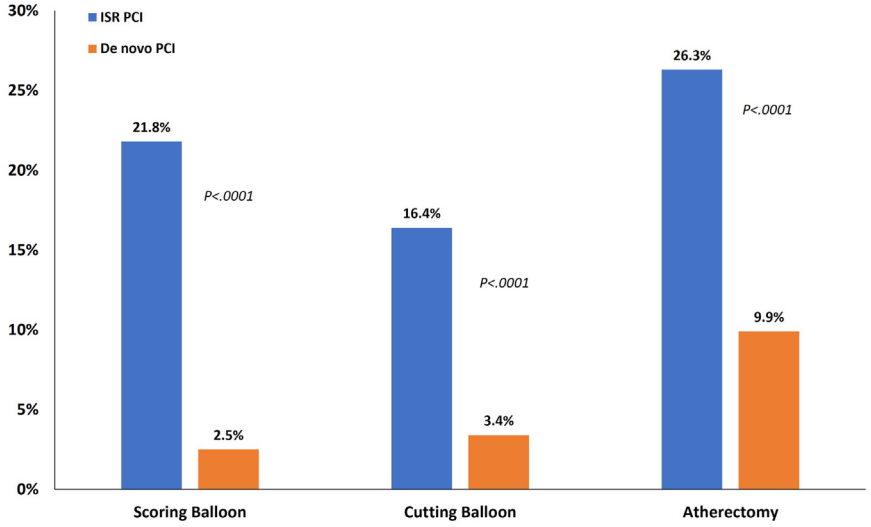
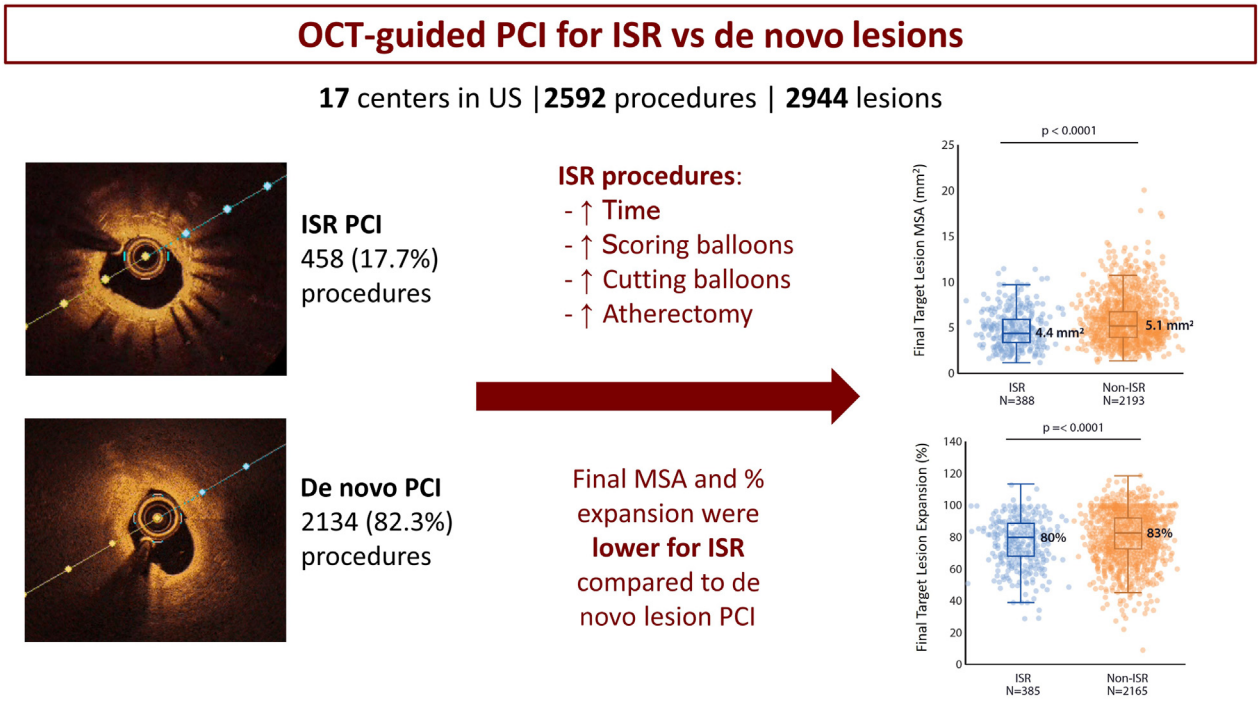


Figure 4.
Lesion preparation device utilization in ISR vs de novo PCI. CABG, coronary artery bypass graft surgery; ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

was final percent expansion. These findings emphasize the difficulty in achieving procedural success in ISR PCI, often due to the constraints of an initially underprepared target lesion at index, or unresolvable stent issues such as gross undersizing. The high incidence of stent failure, complexity of stent failure treatment, and the impact of intravascular imaging on reducing stent failure occurrence ultimately reinforce the importance of performing high-quality PCI initially on de novo lesions.

Study Limitations

While these findings are drawn from a robust, prospective data source incorporating procedures from >40 interventional cardiologists across the United States, there are important limitations. First, although the participating operators were experienced in catheterization laboratory-based research, there is no way to eliminate the potential for observation to influence behavior and decision making. Second, the LightLab Initiative was completed before widespread adoption of coronary intravascular lithotripsy in the United States, and it is not clear how the availability of this treatment modality would impact the findings pertaining to atherectomy. Finally, all operators had some degree of familiarity with OCT. Even so, there was a range of prior experience, and we previously showed that for OCT-based vs angiography-based decision making, there was no significant difference based on physician OCT experience.[8]



Central Illustration.
Procedural success for ISR vs de novo PCI. CABG, coronary artery bypass graft surgery; ISR, in-stent restenosis; OCT, optical coherence tomography; PCI, percutaneous coronary intervention.

Conclusions

In this real-world cohort of nearly 3000 lesions treated with OCT-guided PCI, ISR was common, accounting for 18% of PCIs. ISR procedures were longer in duration and involved significantly greater use of scoring and cutting balloons and atherectomy. Despite increased use of aggressive plaque modification techniques, final MSA and percent expansion were lower for ISR than those for de novo lesions. OCT impacted operator lesion assessment and plan in the vast majority of ISR procedures, indicating the potential importance of using a standardized pre-PCI and post-PCI coronary imaging workflow when treating these challenging lesions.

Acknowledgments

The authors acknowledge all LightLab physicians and their contributions to the study and to the LightLab clinical team in the field.

Declaration of competing interest

Brian Bergmark reports research grants (through the Brigham and Women's Hospital) from Pfizer, Ionis, Quark, AstraZeneca/MedImmune, Abbott Vascular, and Amgen; consulting/personal fees from Philips, Abbott Vascular, CSI, Abiomed, Servier, Janssen, Quark, and Daiichi Sankyo. Jana Buccola, Richard Rapoza, and Nick West are employees of Abbott Vascular. Jason Wollmuth reports honoraria from Abbott Vascular, Boston Scientific, Abiomed, CSI, Philips, and Asahi Intecc. Bassem Chehab is a consultant for and receives speaking fees from Abbott Vascular, CSI, Edwards Lifesciences, and Medtronic. Kevin Croce reports grant support from Abbott, Takeda, Teleflex, and CSI; reports honoraria from Abbott, Biotronik, Philips, Boston Scientific, Abiomed, CSI, Takeda, and Cordis, and is a major stock shareholder in Dyad Medical. Brian Bergmark and Julia Kuder are members of the TIMI Study Group, which has received grant support from Abbott, Amgen, Anthos Therapeutics, AstraZeneca, Bayer HealthCare Pharmaceuticals, Daiichi-Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics, The Medicines Company, and Zora Biosciences.

Funding sources

The LightLab Initiative is a clinical program funded by Abbott Vascular.

Ethics statement and patient consent

Institutional Review Board approval or exemption was obtained at all participating centers, and all appropriate ethical guidelines were followed in the conduct of this study.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.101118.

References

1. Waldo SW, O'Donnell CI, Prouse A, et al. Incidence, procedural management, and clinical outcomes of coronary in-stent restenosis: insights from the National VA CART Program. *Catheter Cardiovasc Interv*. 2018;91(3):425–433.
2. Tamez H, Secemsky EA, Valsdottir LR, et al. Long-term outcomes of in-stent restenosis percutaneous coronary intervention among Medicare beneficiaries. *EuroIntervention*. 2020;17:e380–e387.
3. Giustino G, Colombo A, Camaj A, et al. Coronary in-stent restenosis: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;80(4):348–372.
4. Oyama K, Furtado RHM, Fagundes Jr A, et al. Effect of evolocumab on complex coronary disease requiring revascularization. *J Am Coll Cardiol*. 2021;77(3):259–267.
5. Lee JM, Choi KH, Song YB, et al. RENOVATE-COMPLEX-PCI Investigators. Intravascular imaging-guided or angiography-guided complex PCI. *N Engl J Med*. 2023;388(18):1668–1679.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165.
7. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79(2):197–215.
8. Bergmark B, Dallan LAP, Pereira GTR, et al, LightLab Initiative Investigators. Decision-making during percutaneous coronary intervention guided by optical coherence tomography: insights from the LightLab Initiative. *Circ Cardiovasc Interv*. 2022;15(11):872–881.
9. Raja A, Osborn EA, Bergmark BA, et al. LightLab Clinical Initiative Investigators. OCT utilization: summary statistics from the LightLab clinical initiative. *Catheter Cardiovasc Interv*. 2022;100(suppl 1):S36–S43.
10. Buccola J, Meinen J, Spinelli J, Hammerstone M, Rapoza R, West NEJ. Investigating real-world impact of optical coherence tomography workflow-guided coronary interventions: design and rationale of the LightLab Clinical Initiative. *Catheter Cardiovasc Interv*. 2022;100(suppl 1):S1–S6.
11. Ali ZA, Karimi Galougahi K, Mintz GS, Maehara A, Shlofmitz RA, Mattesini A. Intracoronary optical coherence tomography: state of the art and future directions. *EuroIntervention*. 2021;17(2):e105–e123.
12. Shlofmitz E, Croce K, Bezerra H, et al. The MLD MAX OCT algorithm: an imaging-based workflow for percutaneous coronary intervention. *Cath Cardiovasc Interv*. 2022;100(suppl 1):S7–S13.
13. Bergmark BA, Osborn EA, Ali ZA, et al. Association between intracoronary imaging during PCI and clinical outcomes in a real-world US Medicare population. *J Soc Cardiovasc Angio Interv*. 2023;2(2):100556.
14. Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *J Am Coll Cardiol Intv*. 2019;12(20):1991–2001.
15. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol*. 2018;72(24):3126–3137.
16. Jang JS, Song YJ, Kang W, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *J Am Coll Cardiol Intv*. 2014;7:233–243.
17. Hong SJ, Kim BK, Shin DH, et al, IVUS-XPL Investigators. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA*. 2015;314(1):2155–2163.
18. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. *Circ Cardiovasc Interv*. 2019;12(8), e007023.
19. Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. *EuroIntervention*. 2022;18(2):e103–e123.