ESC
European Society
of Cardiology

Intracoronary imaging to guide percutaneous coronary intervention: from evidence to guidelines

Flavio Giuseppe Biccirè[1,2,3]*, Laura Gatto[1,2], and Francesco Prati[1,2,4]

[1]*Cardiovascular Sciences Department, San Giovanni Addolorata Hospital, Rome;* [2]*Centro per la Lotta contro l'Infarto, CLI Foundation, Rome;* [3]*Dept. of General and Specialized Surgery "Paride Stefanini", Sapienza University of Rome, Rome; and* [4]*Cardiology, UniCamillus, Saint Camillus International University of Health Sciences, Rome*

Despite notable advances in devices and techniques, percutaneous coronary intervention (PCI) is still affected by a substantial number of complications and failure rates. Over the years, the use of intracoronary imaging (ICI) has dramatically improved the understanding of mechanical and technical factors related to successful and failed PCI, becoming a mainstay in complex trans-catheter interventions. However, ICI modalities are invasive, time-consuming, and costly, and a net clinical benefit needs to be shown in order to recommend their routine use in clinical practice. In the past, the lack of evidence from randomized trials has been reflected in the scepticism shown by international guidelines. The recent publication of large randomized clinical trials conducted worldwide has provided new evidence regarding the clinical usefulness of ICI guidance in PCI. The consistent reduction of adverse events achieved in these trials, also demonstrated in an updated meta-analysis, suggested that the use of ICI in PCI is compelling to achieve optimal technical results and better outcomes, especially in complex high-risk interventions. Also considering the burden of information provided by ICI on coronary artery disease, looking from the inside seems today an opportunity that modern cardiology cannot ignore anymore.

Introduction

Percutaneous coronary intervention (PCI) is now widely acknowledged as a safe and effective technique able to increase survival, reduce myocardial infarction (MI) rates, and improve the quality of life of patients with coronary artery disease (CAD). However, despite years of advances and improvements in tools and techniques, PCI is still not free from complications, with about 10% of patients treated with PCI experiencing device-oriented coronary events including stent thrombosis, in-stent restenosis, and disease progression in naive coronary segments left untreated. As such, PCI has struggled to prove non-inferior to coronary artery bypass grafting (CABG) in terms of survival rate or MI reduction in patients with stable CAD and complex coronary anatomy, especially in patients with diffuse disease and left main involvement.[1]

Reasons behind PCI failure are many, but, after the advent of new-generation drug-eluting stents, the major determinants of procedural success remain correct stent sizing, optimal stent expansion, and adequate lesion coverage. Traditionally, interventional cardiologists have assessed these crucial aspects by means of coronary angiography, a technique that is both convenient and low cost as it is also used to perform the diagnostic angiogram of coronary arteries. However, this method does not allow a direct visualization of the vessel wall, but only a coronary lumenogram. In addition, the limited resolution of coronary angiography does not enable a proper assessment of the implanted device and thus of the interaction between the stent struts and the vessel wall.

In this regard, the use of intracoronary imaging (ICI) has been received as essential to overcome the inherent

*Corresponding author. Email: flaviobiccire@gmail.com

limitations of coronary angiography. Years of clinical research with ICI have yielded a wealth of information on the exact mechanisms of PCI success and failure and have suggested the use of ICI to directly optimize stent implantation and reduce stent failure. After 30 years since the first intracoronary image acquired with intravascular ultrasound (IVUS) and 20 years since the first with optical coherence tomography (OCT), ICI has now become a mainstay in complex trans-catheter interventions with a widespread and increasing use. However, these modalities are invasive, time-consuming, and costly, and a net clinical benefit needs to be shown in order to recommend their routine use in clinical practice.

Evidence from the use of intracoronary imaging in percutaneous coronary intervention

In the past, evidence regarding the use of ICI in PCI was mainly provided by landmark observational studies investigating features of suboptimal stent implantation associated with poor clinical outcomes.[2] The identified mechanical and technical factors related to short- and long-term device-oriented clinical events included stent under-expansion, media dissections at stent edges, very large malapposition, and geographic miss.[2,3] Although both IVUS and OCT can provide detailed images of the coronary artery wall, lumen, and stent structure, some differences need to be mentioned. Optical coherence tomography has the advantage of 10 times the resolution of IVUS, allowing for a more accurate assessment of plaque composition but with a shallower image and a greater use of contrast medium. In contrast, IVUS can hardly evaluate vessel wall components, but it enables a complete visualization of the entire vessel cross-section (i.e. plaque burden) and ostium segments and does not require contrast medium. As they are equally capable of assessing vessel lumen, IVUS and OCT have similar definitions for stent under-expansion, a metric that is considered by far the most important feature of suboptimal stent implantation. A suboptimal stent implantation can be considered in the presence of a relative stent under-expansion of <70% or absolute minimum stent area of <4.5 mm^2 at OCT and <5.5 mm^2 at IVUS.[2] Differently, different metrics are adopted for geographic miss. Although an adequate lumen area of references is recommended at both techniques, in IVUS, it is suggested to adequately cover the nearby zones with a plaque burden of ≥40%, while, in OCT, it is suggested to cover nearby fibroatheroma with a lipid arc of >180°.[2]

Against this background, it was hypothesized that stent optimization performed according to ICI findings can lead to improved outcomes and reduced rates of stent failure. This hypothesis has now been tested in five large randomized trials.

Intracoronary imaging guidance for percutaneous coronary intervention: results of large randomized controlled trials

In the first large randomized trial, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions (IVUS-XPL),[4] conducted in South Korea and published in 2015, IVUS guidance was proven to be superior to angiography guidance in terms of reducing target vessel failure (TVF), a composite of cardiac death, target lesion MI, or ischaemia-driven target lesion revascularization (TLR). Among 1400 patients with long coronary lesions (≥28 mm in stent length), IVUS- vs. angiography-guided PCI with drug-eluting stent implantation significantly reduced the rate of 1-year TVF (2.9% vs. 5.8%), mainly driven by a lower risk of TLR (2.5% vs. 5.0%) with a 40% non-significant reduction in cardiac mortality [hazard ratio (HR) 0.60, 95% confidence interval (CI) 0.14–2.52].

The results of the IVUS-XPL trial were corroborated in the ULTIMATE[5] (Intravascular Ultrasound Guided Drug Eluting Stents Implantation in 'All-Comers' Coronary Lesions) trial, a randomized study conducted in eight Chinese centres including 1448 all-comer patients and comparing IVUS vs. angiographic guidance for drug-eluting stent implantation. At 1-year follow-up, a 47% reduction in the primary outcome of TVF [a composite of cardiac death, MI, or target vessel revascularization (TVR)] was observed (5.4% using IVUS vs. 2.9% with angiography alone; *P* = 0.019). The reduction in TVF was driven mainly by a reduction in TVR (2.9% vs. 1.5%; *P* = 0.07), although also cardiac mortality was reduced by 50% (HR 0.5, 95% CI 1.17–1.45).

The first large trial that enrolled patients undergoing OCT-guided PCI was the RENOVATE-COMPLEX-PCI[6] (Randomized Controlled Trial of Intravascular Imaging Guidance vs. Angiography-Guidance on Clinical Outcomes after Complex Percutaneous Coronary Intervention) trial. Patients with complex CAD undergoing PCI were randomized to intravascular imaging-guided PCI (*n* = 1092) vs. angiography-guided PCI (*n* = 547). The trial enrolled only patients with undergoing complex coronary interventions, such as true bifurcations, chronic total occlusion, unprotected left main, long coronary lesions (implanted stent ≥ 38 mm in length), and severely calcified lesions. In the intravascular imaging-guided PCI group, the choice of IVUS or OCT was left to the operator discretion. At 24-month follow-up, ICI guidance was associated with a significantly lower rate of TVF (composite of death from cardiac causes, target vessel-related MI, or clinically driven TVR), and the pre-specified subgroup analysis showed a consistent benefit for ICI guidance regardless of used imaging modality. Noteworthy, the RENOVATE-COMPLEX-PCI trial was the first one showing a significant reduction in cardiac mortality (1.7% vs. 3.8%; HR 0.47, 95% CI 0.24–0.93), whereas target vessel MI and TVR did not differ between groups yet being numerically lower in ICI group.

Recently, a robust piece of evidence was provided by the first two large randomized trials enrolling patients in the Western world, namely OCTOBER[7] (OCT or Angiography Guidance for PCI in Complex Bifurcation Lesions) and ILUMIEN IV[8] (OCT-guided coronary stent implantation compared with angiography).

The OCTOBER[7] trial was a randomized, open-label study conducted at 38 centres in Europe and included 1201 patients with an indication for PCI and a complex lesion located at a coronary bifurcation. At 24-month follow-up, the rate of the primary endpoint (a composite of death from cardiac causes, target lesion MI, or ischaemia-driven TLR) was lower with OCT than with angiography guidance (10.1% vs. 14.1%; HR 0.70, 95% CI 0.50–0.98, *P* = 0.035). During the study procedure, the operators involved in the study used about five to six OCT pullbacks per

intervention to check bifurcation treatment steps, resulting in a longer, but also more effective intervention that was associated with a reduction in mortality by 50%.

The ILUMIEN IV,[8] a prospective, randomized, single-blind trial, involved 80 sites in 18 countries and a total of 2487 patients with medically treated diabetes mellitus or complex coronary artery lesions. At 24-month follow-up, the rate of TVF (a composite of death from cardiac causes, target vessel MI, or ischaemia-driven TVR) was not significantly different between the groups (7.4% vs. 8.2%; HR 0.90, 95% CI 0.67–1.19, $P = 0.45$). Of note, cardiac mortality was numerically lower in OCT group, with a point estimate of approximately 45% consistent with previous trials. In addition, the final minimum stent area was larger in OCT group compared with angiography guidance (5.72 ± 2.04 mm^2 vs. 5.36 ± 1.87 mm^2; $P < 0.001$), resulting in a significantly lower incidence of stent thrombosis at follow-up (0.5% vs. 1.4%; HR 0.36, 95% CI 0.14-0.91).

The apparently negative results of ILUMIEN IV in terms of reduction of the primary clinical endpoint may be mainly explained by the lower complexity of lesions enrolled in the trial. Unlike other OCT trials that focused only on the complexity of the lesion anatomy (such as RENOVATE and OCTOBER), ILUMIEN IV included patients with complex conditions defined by both clinical (i.e. diabetes mellitus) and anatomic characteristics (long, bifurcation, or calcified lesions). Therefore, in contrast to RENOVATE and OCTOBER, ILUMIEN IV enrolled more 'low-risk' lesions, in whom the presence of these high-risk features was poorly represented (0% left main, 10% calcific lesions, 7% chronic occlusions, and 3% bifurcations).

However, it should be emphasized that the point estimate risk reduction in cardiac mortality, MI, and repeated revascularizations was consistent all across the mentioned trials. In a recent meta-analysis, including also these trials, and comparing ICI, functional, or angiographically guided PCI, ICI-guided PCI was associated with a significantly reduced risk of TVF [relative risk (RR): 0.72], cardiovascular death (RR: 0.56), MI (RR: 0.81), stent thrombosis (RR: 0.48), and TLR (RR: 0.75) as compared with angiography alone-guided PCI.[9]

Endorsement in guidelines: current recommendations and potential future scenarios

In modern medicine, guidelines collect evidence to provide recommendations on the clinical utility of a specific treatment or methodology, in order to help physicians and health systems set cost-effectiveness and priorities for better patient treatment. In 2018, the previous Class IIb recommendation for the use of ICI to guide PCI in earlier clinical practice guidelines was upgraded to Class IIa indication in the European guidelines on myocardial revascularization.[10] More recently, the European guidelines on acute coronary syndrome updated the level of evidence from B to A and still confirmed the IIa recommendation for 'PCI guidance'.[11]

The lack of a stronger recommendation by the latest European guidelines was probably due to the scarceness of the data on the European population and specific PCI settings available at the time of defining recommendations. As aforementioned, this gap in

evidence was recently filled by the publication of the results of OCTOBER and ILUMIEN IV.

Considering the results obtained in randomized trials, a possible scenario in the near future is that a Class I recommendation can be provided only for specific settings and high-risk interventions. It is difficult to imagine a strong indication for ICI guidance in *any* PCI. The negative results of ILUMIEN IV were obtained in patients that were selected more for clinical reasons (i.e. diabetes mellitus) rather than lesion complexity. Conversely, the positive results of OCTOBER and RENOVATE were achieved in complex lesions, which emphasize the importance of obtaining ICI images especially when performing complex intervention. Of note, a pre-specified sub-analysis of the RENOVATE trial showed that the largest clinical benefit was shown in the left main intervention.[6]

Thus, a screening of the type of coronary anatomy and the complexity of the lesion to be treated (left main, bifurcation, calcific lesion, chronic occlusion, and long lesions > 3 cm) can help identify patients who can benefit most from ICI-guided PCI. With regard to individual modalities, similar results have been obtained in studies directly comparing IVUS vs. OCT, and the superiority of one technique over the other has never been demonstrated, as in the recently published OCTIVUS study.[12] Rather than mutually exclusive, these two methods appear to be complementary, and the use of one rather than the other depends on the specific case and the expertise of the centre.

Future perspectives

Intracoronary imaging has not only improved the results of coronary intervention but also dramatically changed our understanding of atherosclerotic and non-atherosclerotic CAD.[13] In acute context, intracoronary images can help identify the real lesion culprit of the acute instability and the underlying pathophysiology. Accordingly, in the latest European guidelines on acute coronary syndrome, ICI (preferably OCT) was recommended in patients with ambiguous culprit lesion with a Class IIb indication.

In chronic setting, the accumulating burden of evidence provided by ICI studies is changing established paradigms in clinical practice. So far, PCI in a stable setting has been typically performed as a focal treatment for lesions with obstructive disease shown by invasive coronary angiography or with flow limitation detected by invasive functional measurement. Intracoronary imaging prospective studies have now reportedly shown that also non-flow limiting lesions with a mild encroachment on the arterial lumen, thus not identified as severe by angiography or functional evaluation, can cause events if harbouring high-risk atherosclerotic features.[14,15]

In the FAME 3 trial, fractional flow reserve-guided PCI did not meet the criterion set for non-inferiority vs. CABG with respect to major adverse cardiac and cerebrovascular events at 1 year, including repeat revascularization, and showed a higher incidence of MI at 3-year follow-up.[1] The relatively high incidence of MI in PCI arm is not surprising, as CABG treats a significantly larger portion of the coronary tree, thus potentially protecting not only from events occurring in obstructive lesions but also from those lesions that are non-obstructive at the time of angiography

but at a high-risk of determining events. In the CLIMA study, the presence of lipid-rich non-obstructive coronary lesions with high-risk plaque features, located proximal to stented segments in the left anterior descending artery, was associated with a higher incidence of composite endpoints including cardiac death, target vessel MI, and TVR.[16] Whether a revascularization strategy based on evaluation of plaque composition rather than flow limitation can reduce clinical events is currently unclear and under investigation in ongoing trials such as PREVENT (Clinicaltrials.gov ID: NCT02316886), INTERCLIMA (ClinicalTrials.gov ID: NCT05027984), and COMBINE-INTERVENE (ClinicalTrials.gov ID: NCT05333068). However, evidence has already shown that the risk stratification and plaque-type characterization provided by ICI can identify lesions and patients that may benefit more from potent systemic treatment.[17]

Conclusions

After years of clinical research and a growing body of evidence, the question is set: is the routine use of ICI strongly recommended to guide coronary intervention and improve clinical outcomes? From a simple point of view, it appears logical that observing coronary arteries and stents with ICI is more efficient than relying on a blurry view from the outside. When looking at the evidence, it becomes even clearer that ICI guidance positively affects the outcomes of patients undergoing complex coronary intervention. Using ICI during coronary intervention can not only verify the correctness of stent implantation but also influence patient outcomes by improving risk stratification. Even if an upgrade of guidelines is still uncertain, one thing appears clear: the impact of ICI in modern cardiology has just begun.

Funding

Data availability

No new data were generated or analysed in support of this research.

References

1. Zimmermann FM, Ding VY, Pijls NHJ, Piroth Z, van Straten AHM, Szekely L *et al.* Fractional flow reserve-guided PCI or coronary bypass surgery for 3-vessel coronary artery disease: 3-year follow-up of the FAME 3 trial. *Circulation* 2023;**148**:950-958.
2. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y *et al.* Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J* 2018;**39**:3281-3300.
3. Prati F, Romagnoli E, Biccirè FG, Burzotta F, La Manna A, Budassi S *et al.* Clinical outcomes of suboptimal stent deployment as assessed by optical coherence tomography: long-term results of the CLI-OPCI registry. *EuroIntervention* 2022;**18**:e150-e157.
4. Hong SJ, Kim BK, Shin DH, Nam CM, Kim JS, Ko YG *et al.* Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JAMA* 2015;**314**:2155-2163.
5. Zhang J, Gao X, Kan J, Ge Z, Han L, Lu S *et al.* Intravascular ultrasound versus angiography-guided drug-eluting stent implantation: the ULTIMATE trial. *J Am Coll Cardiol* 2018;**72**:3126-3137.
6. Lee JM, Choi KH, Song YB, Lee JY, Lee SJ, Lee SY *et al.* Intravascular imaging-guided or angiography-guided complex PCI. *N Engl J Med* 2023;**388**:1668-1679.
7. Holm NR, Andreasen LN, Neghabat O, Laanmets P, Kumsars I, Bennett J *et al.* OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med* 2023;**389**:1477-1487.
8. Ali ZA, Landmesser U, Maehara A, Matsumura M, Shlofmitz RA, Guagliumi G *et al.* Optical coherence tomography-guided versus angiography-guided PCI. *N Engl J Med* 2023;**389**:1466-1476.
9. Kuno T, Kiyohara Y, Maehara A, Ueyama HA, Kampaktsis PN, Takagi H *et al.* Comparison of intravascular imaging, functional, or angiographically guided coronary intervention. *J Am Coll Cardiol* 2023;**82**:2167-2176.
10. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87-165.
11. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A *et al.* 2023 ESC guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;**44**:3720-3826.
12. Kang DY, Ahn JM, Yun SC, Hur SH, Cho YK, Lee CH *et al.* OCTIVUS investigators. Optical coherence tomography-guided or intravascular ultrasound guided percutaneous coronary intervention: the OCTIVUS randomized clinical trial. *Circulation* 2023;**148**:1195-1206.
13. Arbustini E, Morbini P, Dal Bello B, Prati F, Specchia G. From plaque biology to clinical setting. *Am Heart J* 1999;**138**:S55-S60.
14. Kedhi E, Berta B, Roleder T, Hermanides RS, Fabris E, IJsselmuiden AJJ *et al.* Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. *Eur Heart J* 2021;**42**:4671-4679.
15. Prati F, Romagnoli E, Gatto L, La Manna A, Burzotta F, Ozaki Y *et al.* Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;**41**:383-391.
16. Biccirè FG, Budassi S, Ozaki Y, Boi A, Romagnoli E, Di Pietro R *et al.* Optical coherence tomography-derived lipid core burden index and clinical outcomes: results from the CLIMA registry. *Eur Heart J Cardiovasc Imaging* 2023;**24**:437-445.
17. Biccirè FG, Häner J, Losdat S, Ueki Y, Shibutani H, Otsuka T *et al.* Concomitant coronary atheroma regression and stabilization in response to lipid-lowering therapy. *J Am Coll Cardiol* 2023;**82**:1737-1747.