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Systematic Review

Advancements in Intravascular Coronary Imaging: The Role of IVUS, OCT, and Emerging Multimodal Technologies in Optimizing PCI Outcomes

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Abstract

Intravascular imaging has revolutionized the management of coronary artery disease through enhanced plaque characterization and the optimization of percutaneous coronary interventions. In this review, the two most important intravascular imaging modalities—intravascular ultrasound (IVUS) and optical coherence tomography (OCT)—are discussed, with new, evolving multimodality technologies such as near-infrared spectroscopy (NIRS), near-infrared fluorescence (NIRF), and their hybrid systems—NIRS-IVUS and OCT-IVUS. Since its introduction, IVUS has contributed to great benefits in guiding PCI, especially for complex lesions, improving stent expansion, and reducing major adverse cardiovascular events. Recent trials have reinforced its role in reducing target lesion revascularization and stent thrombosis in CTOs, bifurcations, and left main coronary artery diseases. High-resolution OCT visualizes stent struts, plaque morphology, and the appearance of fibrous caps; eventually, its gains will have to be tested for long-term outcomes in further clinical trials. Hybrid systems, such as NIRS-IVUS and NIRF-OCT, hold promise for combining structural and molecular insights, but their full clinical validation has yet to be performed. It is expected that, by 2024, IVUS in PCI will be widely supported, especially for complex cases, while further data may provide significant contributions from OCT and other newer modalities. This review highlights the clinical value, current limitations, and future potential of intravascular imaging systems and highlights the need for their wider adoption and standardization in clinical practice.

Keywords: Optical Coherence Tomography (OCT); Near-Infrared Fluorescence (NIRF)

Introduction

Despite its many limitations, CAG has remained the clinical gold standard for diagnosing CAD [1]. While CAG clearly delineates the coronary lumen, it is insensitive to the arterial wall itself, which is extremely important in the origin and progression of CAD [1]. By overcoming these limitations, high-resolution intracoronary imaging techniques have been developed with the promise of obtaining a more complete picture of the vessel. Intravascular ultrasound, which has been in use for several decades, is a game changer in the assessment of PCI, yielding important information on stent expansion, dissections of the arterial wall, and tissue prolapse [2,3]. Important information regarding the characteristics of atherosclerosis, such as plaque calcification, plaque burden, severity of left main CAD, and vessel geometry assessment, is also given by IVUS [4]. Within the past several years, OCT has emerged as a high-resolution alternative to IVUS [4]. Most recently, OCT imaging has achieved a resolution tenfold greater than that of conven-

tional IVUS and fivefold greater than that of even HD-IVUS [5]. Thus, detailed visualization of the stent struts, arterial dissections, and detailed plaque composition, including the fibrous cap, lipids, calcium deposits, and thrombus, is possible. Furthermore, OCT has been found to be better able to detail the mechanisms of stent failure, such as fracture, deformation, or recoil, which are less apparent with IVUS (Figure 1) [6]. In 2024, a new wave of imaging modalities further expanded the landscape of coronary imaging, which is no longer restricted to near-infrared spectroscopy and near-infrared fluorescence imaging, which is now favored and enables simultaneous assessment of both structural and molecular features of atherosclerotic plaques [7]. Lipid-rich plaques can be detected via NIRS, and NIRF imaging can estimate both inflammatory activity and intraplaque hemorrhage on the basis of near-infrared autofluorescence. These new modalities represent especially promising ways of recognizing high-risk plaques that are susceptible to either progression or atherothrombosis. Finally, in 2024, an accumulation of evidence, most of which is from large-scale perspective RCTs, goes on to elicit clinical benefits from intravascular imaging [8]. IVUS-guided PCI has demonstrated benefits in terms of improvements in procedural outcomes, particularly for complex lesion subsets, by reducing clinical restenosis and MACE rates [9]. More recent trials performed with OCT confirm its potential for optimizing stent deployment and adverse clinical outcomes. In this respect, OCT has been established as an important tool for improving long-term results in PCI [10]. The combination of NIRS with IVUS has also emerged as a formidable hybrid modality offering both structural and compositional plaque assessment for better prediction of future coronary events. Despite the growing evidence that supports the routine use of IVIs, adoption remains spotty, with marked variability depending on the expertise of the operator, geographic location, and available resources at the institution [11]. These challenges have created a newly heightened emphasis on advanced IVI techniques in interventional cardiology training to ensure that future practitioners are competent in image acquisition, interpretation, and clinical integration. In this review, we review the current state-of-the-art in intravascular coronary imaging, focusing on IVUS, OCT, and emerging multimodal imaging techniques. We review the recent clinical evidence supporting their use, emphasize current limitations, and consider future directions for further optimizing coronary imaging in clinical practice.

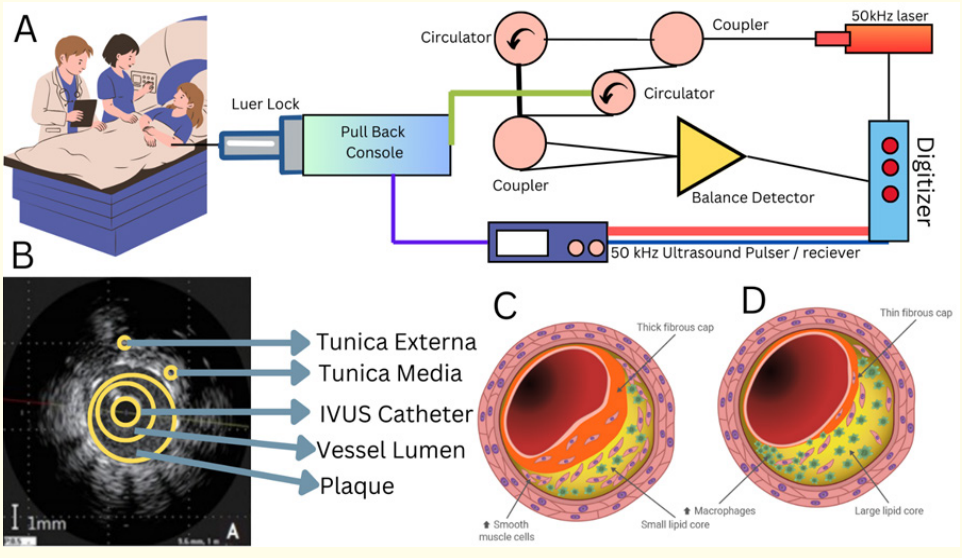

Figure 1: Mechanism and visualization of intravascular ultrasound (IVUS) imaging and plaque characteristics. (A) Schematic diagram of the working mechanism of an intravascular ultrasound (IVUS) imaging system. The pullback console controls the catheter's movement through the vessel, while ultrasound signals are transmitted and received by a 50 kHz pulser. A circulator system directs signals to a digitizer for image reconstruction, offering detailed cross-sectional images of the vessel. (B) Real IVUS cross-sectional image showing the layers of the artery, including the tunica externa, tunica media, vessel lumen, and atherosclerotic plaque surrounding the vessel. The IVUS catheter is positioned in the center of the vessel, allowing visualization of plaque buildup. (C) Schematic representation of a normal plaque, characterized by a thick fibrous cap and a small lipid core. Smooth muscle cells are present in the vessel wall, stabilizing the plaque and reducing the likelihood of rupture. (D) Schematic representation of a vulnerable plaque characterized by a thin fibrous cap and a large lipid core. Macrophage infiltration is prominent, increasing the risk of plaque rupture and subsequent cardiovascular events [81].

Advances in IVUS imaging

Clinical outcome studies Intravascular ultrasound, introduced in 1990, enabled the first visualization of intracoronary plaque characteristics and vessel morphology. Early RCTs comparing IVUS-guided PCI with CAG-guided PCI demonstrated neutral effects on MACEs [12]. The HOME DES IVUS trial revealed that at 18 months, there was no difference in MACEs or stent thrombosis; however, higher postdilation pressures were observed in the IVUS group [13]. Similarly, no significant reduction in MACEs at 1 year was noted in the study by Kim., *et al*. because of the small sample size and crossover of patients [14]. In the AVIO trial, the postprocedural minimal lumen diameter (MLD) was identified as the primary endpoint, which demonstrated larger MLDs among IVUS-guided PCI patients, although with similar MACE rates [15].

Larger and more robust studies have been conducted since 2019 to reinforce the clinical benefits of IVUS [16]. In fact, the results of the ULTIMATE trial in 2019 demonstrated a significant reduction in target vessel failure and improved outcomes with IVUS-guided PCI, especially with second-generation DES [17,18]. More contemporary trials, such as IVUS-XPL, have only served to further consolidate the role of IVUS in reducing stent failure and thus improved clinical outcomes, demonstrating significantly lower MACE rates, including decreased target vessel revascularization and stent thrombosis, relative to those of angiography-guided PCI [19]. These data indicate that modern trials with larger sample sizes and better study designs overcome the limitations of previously conducted research.

In 2024, IVUS played a paramount role in stent deployment optimization, ensuring proper stent expansion, underexpansion reduction, and complications such as dissection or incomplete lesion coverage [20]. Its adoption ensured better procedural success with fewer long-term complications in complex lesion subsets, such as left main coronary artery disease, long lesions, chronic total occlusions, and bifurcations. In the left main CAD artery, where the precision of stent placement is a matter of vital importance, IVUS has established particular benefit in the prevention of adverse outcomes [21].

By 2024, there is an increasing recommendation for IVUS guidance in managing complex PCIs. It is also included in the guidelines of both Europe and America for left main and complex coronary disease [22]. While benefits from IVUS have, for the most part, been almost innumerable, its use still varies widely and is partly dependent on operators' experience and available resources [23]. Standardization of its usage is also still largely at the development stage, and only recently has there been an increased emphasis on training during interventional cardiology fellowships to prepare practitioners in the future who will be able to use this technology to its full advantage.

RCT of IVUS in long lesions

A number of trials have investigated the impact of IVUS-guided PCI in long lesions. The IVUS-XPL trial randomized 1400 patients with target lesion lengths ≥28 millimeters and symptoms of chest pain or ischemia to either IVUS-guided PCI with everolimus-eluting stents or CAG-guided PCI [24]. The major adverse cardiovascular events, which included cardiac death, MI, and TLR, were reduced by IVUS guidance from 5.8% to 2.9%, driven mostly by a 50% reduction in TLR [25]. Kim., *et al*. also evaluated IVUS-guided PCI for long lesions but reported no significant reduction in MACE in the intention-to-treat analysis because of high crossover rates [26]. Nonetheless, in the on-treatment analysis, it decreased from 8.1% to 4.0%, driven by fewer target-vessel revascularizations. Updated trials up to 2024 have further confirmed this benefit in long lesions, with newer studies reporting improved stent expansion and fewer complications [27]. Recent meta-analyses have confirmed that IVUS-guided PCI significantly reduces the incidence of restenosis and adverse events for long lesions, reinforcing its role as the preferred guidance modality in complex cases of PCI, especially for lesions > 30 mm [28]. RCT of IVUS in Chronic Total Occlusion PCI Two large trials have examined IVUS-guided PCI for CTOs [29]. The CTO-IVUS trial, which randomized 402 subjects to undergo either IVUS or CAG-guided PCI, demonstrated a >50% reduction in MACE (7.1% to 2.6%) at 12 months, driven by significant reductions in cardiac death and MI, although not in TVR [30]. This latter observation is remarkable given that the majority of other IVUS trials demonstrate reductions primarily in TVR. The results from the AIR-CTO trial, which randomized 230 patients with successfully crossed CTOs to either IVUS or CAG guidance, demonstrated a significant reduction in in-stent late lumen loss at 12 months but no reduction in MACE because of underpowering for this endpoint [31]. IVUS provides further value in CTO PCI in determining the resolution of proximal cap ambiguity, facilitating real-time wire crossing of CTOs, and confirming wire positioning in true versus false lumens [32]. RCTs of IVUS in All-Comers Most IVUS trials are either non-

randomized or focused on anatomical outcomes such as MLD [33]. In contrast, the ULTIMATE trial included 1,448 "all-comers" who underwent PCI with DES without specific lesion restrictions [34]. IVUS-guided PCI significantly reduced TVF from 5.4% to 2.9% at 1 year, driven by reductions in TVR and numerically lower rates of cardiac death and target-vessel MI [35]. Moreover, this trial was able to confirm the benefit of intravascular US-guided stent sizing and optimization. By 2024, newer studies have continued to outline the benefits of IVUS in PCI [36]. A recent meta-analysis included data from ULTIMATE and other trials and revealed a 38% reduction in MACE, 49% in cardiovascular death, and 42% in TVR [37]. Coupled with a trend toward reduced MI, these results cemented IVUS as a very important tool in modern-day PCI, even among more complex and high-risk populations [38]. Newer trials now aim to expand its indication in CTOs and long lesions, further validating the indication of this technology for diverse lesion subsets.

RCT of IVUS in the left main coronary artery

A number of observational studies have demonstrated the clinical value of IVUS for diagnosing significant LM stenosis as well as optimizing LM PCI (Figure 2). These observations constitute the background for the Class IIa recommendation for IVUS in the US guidelines for indeterminate LM assessment and in the European guidelines for LM PCI guidance. Very recently, two small single-center RCTs have evaluated IVUS-guided LM intervention. One randomized trial evaluated 123 elderly patients (>70 years); IVUS significantly reduced MACE at 2 years, largely due to a reduction in TLR [39]. Another published RCT of 336 patients demonstrated a significant reduction in the 1-year composite MACE endpoint from 21.9% to 13.2% with IVUS guidance [40]. A meta-analysis of 4,592 patients included one RCT and six observational studies confirming the benefit of IVUS in LM PCI [41]. It significantly reduces MACE (39%), all-cause mortality (45%), cardiac death (55%), myocardial infarction (34%), and stent thrombosis (52%) [42]. Although the reductions in TLR and TVR did not reach statistical significance in this meta-analysis, both RCTs were consistent in that they demonstrated that IVUS guidance lowered the revascularization rates [43]. These findings further establish IVUS as a valuable tool for optimizing LM PCI outcomes.

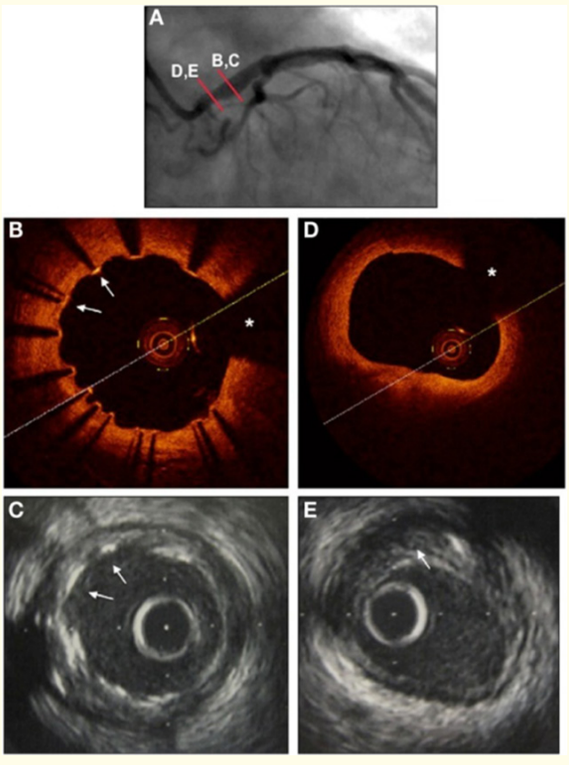

Figure 2: Imaging of the left main coronary artery via angiography, OCT, and IVUS. (A) Coronary angiography from the RAO view, showing a mild proximal left main lesion and a drug-eluting stent in the middle and distal portions of the left main coronary artery. (B) OCT of the middle left main artery, showing well-apposed stent struts to the vessel wall with clear visualization (arrows) and a wire artifact shadow marked with an asterisk. (C) IVUS of the same site in the middle left main artery, showing stent struts, although with less precision than OCT (arrows). (D) OCT of the left main ostium, showing a clear lumen (calculated at 7.1 mm^2) but without detail on the underlying plaque. (E) IVUS of the left main ostium, showing both the lumen (calculated at 6 mm^2) and the extent of the underlying plaque, marked with an arrow (40% area stenosis) [82].

Additional IVUS prospective, nonrandomized outcomes studies of importance bifurcations

Compared with nonbifurcation lesions, stented bifurcation lesions are known to carry an increased hazard of target lesion failure. The role of IVUS in bifurcation percutaneous coronary intervention has been studied, as complex anatomy often complicates stent deployment in the setting of bifurcation lesions [44]. A study compared IVUS-guided vs. CAG-guided two-stent techniques for coronary bifurcation lesions and reported a significant reduction in stent thrombosis and MI, although there was no overall MACE difference, including TLR [45]. In a study by Chen., *et al*. 1,465 patients with unstable angina and Medina 1,1,1 or 0,1,1 bifurcation lesions were enrolled in a 7-year follow-up [46]. IVUS-guided PCI significantly reduced MACE (cardiac death, MI, target vessel revascularization [TVR]) from 15% to 10% at 1 year and from 22.4% to 15% at 7 years. Consequently, IVUS guidance significantly reduced cardiac death, from 6.5% to 1.3%, and myocardial infarction, from 8.4% to 2.3%. These findings underscore the increasing role of IVUS in improving the outcomes of complex bifurcation percutaneous coronary intervention, particularly over long-term follow-up.

By 2024, IVUS will continue to evolve in the treatment of bifurcation lesions. Newer studies demarcate improved outcomes using hybrid imaging, such as IVUS, in combination with OCT for the treatment of bifurcation lesions [47]. These newer techniques provide exquisite delineation of the anatomy of the bifurcation, hence enabling optimal positioning of the stent with minimal edge dissections. Furthermore, recent registry data confirm that IVUS-guided bifurcation PCI in both the left main and nonleft main settings results in even lower rates of long-term adverse events, thus confirming its role in complex coronary interventions.

Cost-effectiveness

These findings concerning cost-effectiveness, particularly in high-risk populations, have been reproduced through various single- and multicenter studies, most of which, before the trials demonstrated reduced MACE, are likely underestimating the full cost-effectiveness of IVUS. For example, in the ULTIMATE trial, there was a small increase in the use of contrast agent (17 ml), but this increase was offset by significant clinical benefits [48]. Clinical practice often allows IVUS to reduce contrast exposure by optimizing stent placement and minimizing additional interventions.

In 2024, as experience and advancements in IVUS technology advanced, the procedural time will likely decrease and become more efficient. However, there is an increase in the procedural time of approximately 15 minutes, but this increase is acceptable given the substantial clinical benefits accrued, particularly with regard to complex cases. This time may decrease with increasing routine use and familiarity with IVUS as technology and experience advance.

Value-added and cost-effective IVUS may be regarded as such a modality in contemporary interventional cardiology, given that it is able to improve long-term outcomes. An important evolution in IVUS technology is represented by HD IVUS catheters with a 60-MHz frequency instead of the standard 40 MHz frequency (Figure 3) [49]. These catheters improve the resolution and allow faster pull-back speed. Indeed, the renovated resolution allows a better depiction of fibrous and lipidic plaque, tissue prolapse, and strut malposition while still maintaining high depth penetration in comparison with OCT [50]. HD-IVUS has shown increased detailed imaging of bioresorbable scaffold struts compared with conventional IVUS [51]. However, OCT is still the best modality for assessing stent thrombotic material, stent malposition, and fibrous cap and calcium thickness.

Stent optimization via IVUS

The key benefits of the use of IVUS include the optimization of stent implantation. IVUS-guided PCI can be used to evaluate stent expansion, plaque burden, and appropriate edge conditions, such as lipid pools or edge dissections, which are critical for long-term success of the stent. More challenging to assess by IVUS, other important conditions include malposition and tissue protrusion. Stent under expansion is a significant predictor of stent failure. Clinical trials have variably defined optimal stent expansion with MSA thresholds of 80–90% of the RLA [52]. Most recent consensus guidelines suggest that an MSA of > 80% is beneficial and realistically achievable [52]. A plaque burden greater than 50% at the stent edge and large edge dissections have been associated with increased MACE and early stent thrombosis, respectively (Figure 4).

IVUS in Practice 2024 updated trials, such as ULTIMATE, IVUS-XPL, and trials by Chen., *et al*. provided evidence that IVUS-guided PCI reduces MACE, and each trial included more than 1,000 pa-

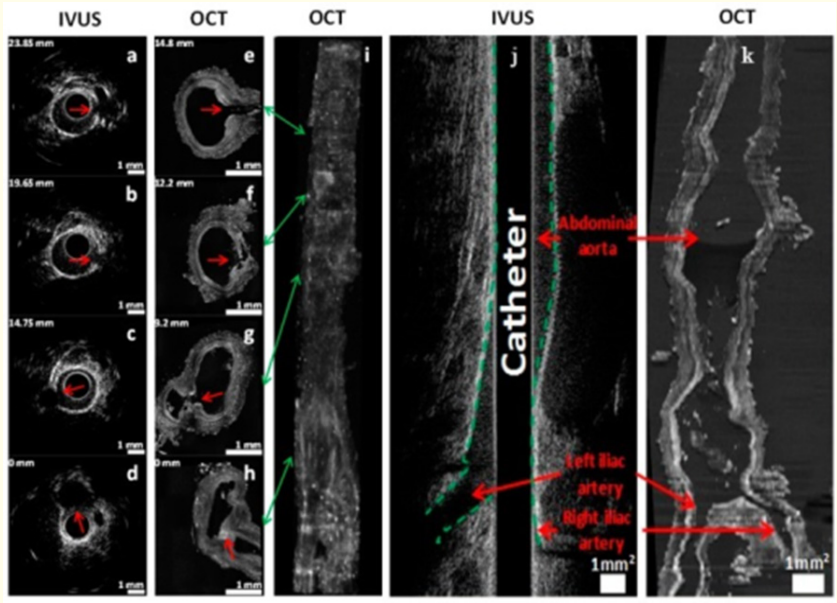

Figure 3: Colocalization of Anatomical Landmarks via IVUS and OCT. (a–d) In vivo IVUS cross-sectional images. (e–h) Ex vivo OCT cross-sectional images showing similar anatomical landmarks. (i) 3D reconstruction of the iliac artery via OCT, with numbers indicating distances from the iliac bifurcation. The green arrows indicate the cross-sectional locations on the 3D reconstruction. Red arrows mark side branches used for colocalization of IVUS and OCT [83].

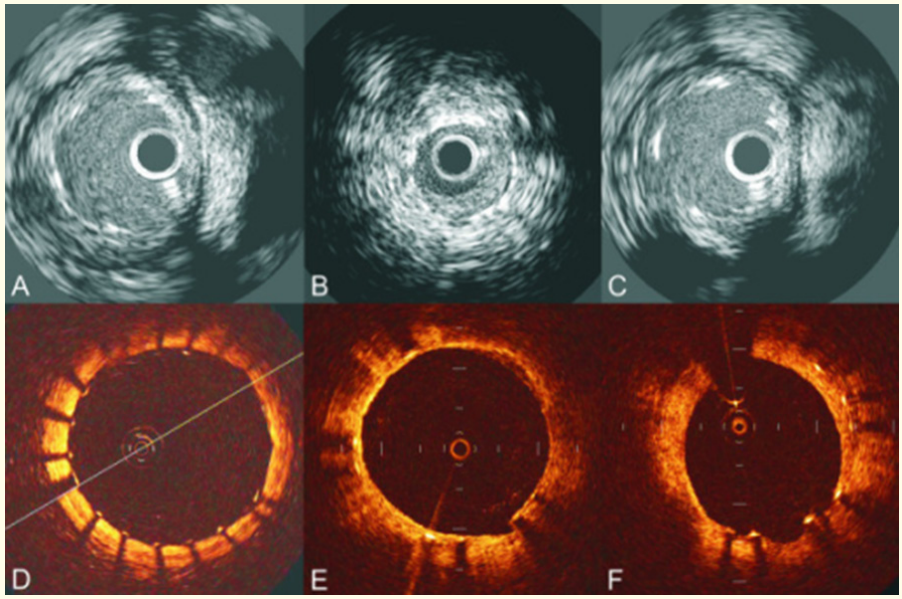

Figure 4: Stent expansion and neointimal formation assessed by IVUS and OCT. (A) IVUS image showing optimal stent expansion. (B) Neointima formation at 6 months after drug-eluting stent (DES) implantation. (C) Late stent malapposition detected by IVUS. (D) OCT image showing the absence of stent strut coverage. (E) OCT image showing complete stent strut coverage. (F) Measurement of neointimal hyperplasia by OCT [84].

tients [52]. This finding established IVUS as an essential tool for stent optimization and improvement in clinical outcome.

It is particularly useful in patients at greater risk for restenosis, including those with diabetes, CKD, ACS, multivessel disease, bifurcation lesions, long lesions, and CTOs. Evidence up to 2024 would support considering IVUS in an even wider range of patients; its indications probably extend to all-comers for the purposes of optimizing stent outcomes and minimizing complications.

Improvements in IVUS

HD IVUS catheters using a 60-MHz frequency compared with the standard 40 MHz frequency have been among the major developments in IVUS. These catheters allow for increased resolution, faster pullback speeds of up to 10 mm/s, and a higher frame rate of 60 frames/s [53]. With improved resolution, there is better visualization of fibrous and lipidic plaques, tissue prolapse, and stent strut malposition while maintaining IVUS's superior depth penetration compared with OCT [54]. HD-IVUS has distinct advantages over conventional IVUS for the clear visualization of bioresorbable scaffold struts, but OCT still remains superior for the assessment of stent thrombotic material, stent malposition, and fibrous cap and calcium thickness. IVUS for Stent Optimization In addition, another primary advantage of IVUS is its ability to optimize stent implantation. IVUS-guided PCI can assess stent expansion, plaque burden, and edge conditions, such as lipid pools or edge dissections—all critical components for long-term success of the stent. Malposition and tissue protrusion, though more challenging to assess with IVUS, are also important considerations. Stent expansion is one of the most significant predictors of stent failure. The consensus on what constitutes optimal stent expansion in clinical trials has varied, with minimum stent area thresholds of 80–90% of the average RLA [55]. Among the most recent consensus guidelines, most suggest that attaining an MSA > 80% is beneficial and realistically achievable. A plaque burden > 50% at the stent edge and large edge dissections have been associated with increased MACE and early stent thrombosis, respectively [56]. IVUS in Practice 2024; Update Collectively, the mentioned RCTs, such as ULTIMATE, IVUS-XPL, and studies by Chen., *et al*. illustrated that IVUS-guided PCI reduced MACE, while all trials enrolled over 1,000 patients [57]. Overall, these trials concluded that IVUS is helpful in optimizing stent implantation, thus resulting in better clinical outcomes. These patients receive the most benefit from IVUS: those with diabetes, CKD, ACS, multivessel disease, bifurcation lesions, long lesions, and CTOs. Evidence up to 2024 still supports the consideration of IVUS in an ever-fairer range of patients, perhaps for all-comers in view of optimizing stent outcomes and minimizing complications during PCI.

Advances in OCT imaging

OCT works on the principle of using near-infrared light, with a wavelength of approximately 1310 nm, to acquire high-resolution pictures of the arterial wall. In comparison, while IVUS has a resolution power of 100–200 μm, OCT has a resolution power of 10–20 μm and is thus far more sensitive in the detection of plaque fibrous caps, thrombi, dissections, and stent strut coverage. High resolution further allows differentiation between plaque erosion and rupture. In short, the higher contrast provided with OCT allows for better detection of lipid-rich plaques and, in some instances, better evaluation of calcium volume. However, for deeper structures of the artery, IVUS is superior because it provides deeper penetration. By default, however, OCT is limited to the assessment of full-wall structure and is, therefore, less effective in plaque burden assessments and often results in smaller stent sizes than IVUS. In addition, OCT requires contrast flushing; hence, patients susceptible to contrast-induced AKI are at risk.

RCTs of OCT

RCT of the OCT against CAG with FFR as a surrogate endpoint, the randomized multicenter Does Optical Coherence Tomography Optimize Results of Stenting (DOCTORS) trial, in fact, assigned 240 patients with non-ST-elevation ACS via a computer-generated randomization list either to OCT-guided or CAG-guided PCI [58]. The main endpoint, which was the post-PCI FFR, increased from 0.92 in the CAG-guided group to 0.94 in the OCT-guided group [59]. OCT identified more stents under expansion malposition and edge dissection, which led to more postdilation and less residual stenosis. However, the clinical relevance of the modest improvement in the FFR remains questionable; the general utility of the FFR as a post-PCI marker of success is still under investigation in trials such as the DEFINE PCI [58].

RCT OCT versus IVUS - Clinical endpoints

The pivotal OPINION trial randomly assigned 829 patients with stable or unstable angina to either OCT-guided or IVUS-guided PCI

with second-generation DES [59]. The primary endpoint of 1-year TVF was similar in the OCT and IVUS arms, unlike the lack of difference in MACE, which was due to overall low event rates and comparable post-PCI MLD between the arms [60].

RCT of OCT versus IVUS versus CAG—Clinical endpoints

In the ILUMIEN III study, 450 patients were randomized to CAG-, IVUS-, or OCT-guided PCI, and the minimal stent area was noninferior to that of CAG according to OCT [61]. OCT revealed the highest number of cases of stent malposition and dissections. These advantages will probably permit the identification of markers for future adverse events, although it remains to be elucidated whether these findings will translate into long-term clinical benefits.

OCT: Advancing the Art 2024 update

Ongoing trials such as ILLUMIEN IV are expected to yield more conclusive data on whether OCT can be translated into improved clinical outcomes by 2024 [62]. The role of OCT in complex lesion assessment has also expanded, with recent emerging evidence demonstrating its superiority in identifying vulnerable plaque features such as thin-cap fibroatheromas that may guide more tailored therapeutic approaches. However, reliance on the use of contrast flushing is one limitation, especially in patients with renal impairment. Whether the higher resolution obtained by OCT will translate to superior long-term clinical benefit obtained by IVUS remains part of the debate.

Future OCT studies

Until recently, there have been few data demonstrating the clear clinical benefit of OCT beyond surrogate markers, and additional trials need to be conducted fully to establish its role in improving outcomes. The ILUMIEN IV is a key current trial that randomizes up to 3,650 high-risk patients to OCT-guided versus CAG-guided percutaneous coronary intervention (PCI) using everolimus-eluting stents in a 1:1 ratio [62]. The primary endpoint is a composite of cardiac death, target-vessel MI and target-vessel revascularization at 2 years. A central focus of interest in the trial is to optimize stent sizing on the basis of EEL-derived measurement, allowing for more precise stent deployment strategies. Two important outcomes of this trial will undoubtedly play a role in driving wider adoption of OCT for clinical use. Moreover, OCT becomes even more significant as the clinical importance of its ability to detect specific features, such as plaque erosion, is established. Pathologically, erosion is a distinct complication of plaques from rupture. Initial reports indicate that plaques complicated by erosion may not necessarily necessitate PCI. These patients could be adequately treated with dual-antiplatelet therapy and glycoprotein IIb/IIIa inhibitors. If confirmed by ongoing studies, OCT may be of pivotal value in deciding the treatment strategy in patients with ACS.

Imaging of arterial lipids and pathobiology by multimodality

While both IVUS and OCT are powerful tools, they cannot detect vulnerable plaques effectively or have predictive value for future cardiovascular events. In the PROSPECT trial, only 18.2% of the positive predictive value could be identified through IVUS-derived variables for lesions that would eventually result in future events [63]. For the PREDICTION trial, the addition of endothelial shear stress to IVUS-derived variables increased the positive predictive value to 41% in predicting which lesions would progress to require revascularization [64]. Although this represents an advance, it outlines the limitations of current imaging techniques and therefore highlights the need for more sophisticated techniques that can precisely define high-risk plaques and open ways for multimodality imaging.

NIRS-IVUS

NIRS identifies lipid-rich plaques on the basis of the content of lipids within them, but it does not have the structural resolution needed for detailed plaque assessment (Figure 5) [65]. In this context, NIRS has been coupled with 50-MHz rotational IVUS in a single 3.2 Fr catheter, which forms the NIRS-IVUS system. To date, the NIRS-IVUS system has achieved clinical clearance in the USA, Europe, Japan, and Korea. Initial reports suggest that culprit lesions in acute coronary syndrome often have increased lipid burdens [66,67]. The NIRS-IVUS system has also been shown to be useful for detecting vulnerable plaques likely to cause future events [68]. Two major trials have tested this theory. The Lipid-Rich Plaque LRP Study NCT02033694 investigated stable patients with ACS with stable angina or a positive functional study [69]. It has also been reported that patients with a maxLCBI4 mm > 400 had an increased risk of NC-MACE at 24 months by 87% [70]. Coronary segments with maxLCBI4 mm > 400 also presented a 4-fold increased risk of NC-MACE [71]. This suggests that NIRS-IVUS may identify high-risk, no culprit arteries; further data on lesion-specific predictive value are awaited. Another ongoing trial, the PROSPECT II trial (NCT02171065), is investigating NC-MACE in ACS patients, whose results are awaited soon after [72].

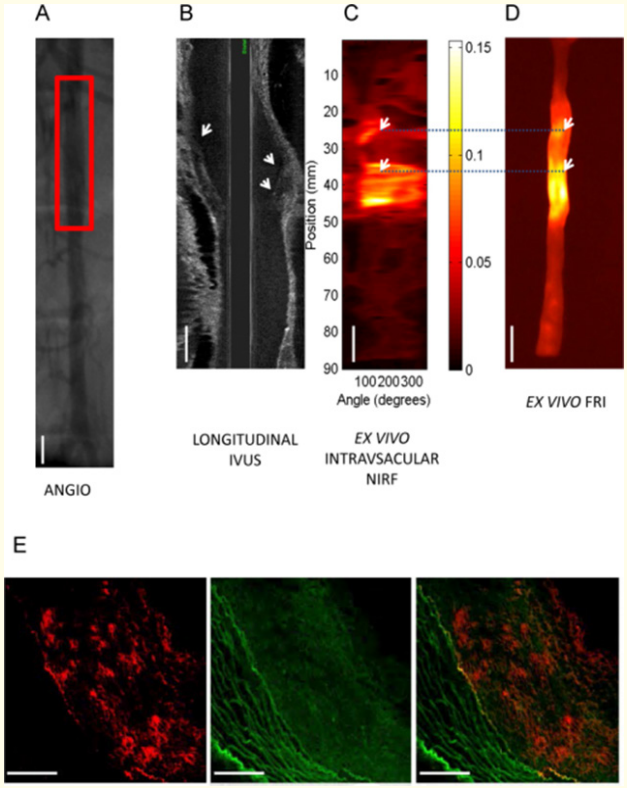

Figure 5: NIRS-IVUS Imaging of Lipid-Rich Plaques in a Rabbit Aorta. (A) Angiography of the rabbit aorta showing the area of balloon injury. (B) IVUS pullback through the aorta showing eccentric atherosclerotic plaques (white arrows). (C) Ex vivo 2D NIRF imaging of LO1-750 localization in the aortic plaque. Two "hot spots" are visible (white arrows). (D) Corresponding ex vivo fluorescence reflectance imaging (FRI) image showing augmented NIRF activity in the same regions. (E) Fluorescence microscopy image showing the localization

Despite the ability of NIRS-IVUS to identify high-risk plaques, many studies are still needed to determine whether intervention in these vulnerable plaques would improve outcomes. Early evidence revealed that medical therapy [73] or stenting [74] may be effective interventions (Figure 6). However, the depth information provided by IVUS mitigates the limitations of NIRS, particularly the inability of NIRS to differentiate superficial lipids from deep lipids due to a lack of depth resolution. NIRF Molecular and Intraplaque Hemorrhage (IPH) Imaging Fortunately, NIRF imaging of coronary arteries allows molecular imaging via specific near-infrared fluorescence agents, which can be visualized via an intravascular NIRF catheter. To carry both molecular and structural information, NIRF has been incorporated into hybrid systems with IVUS (NIRF-IVUS) [75] and OCT (NIRF-OCT) [76]. Because NIRF does not provide depth resolution, the molecular signals are projected onto the anatomical structures imaged by either IVUS or OCT. OCT-NIRF has been reported to quantify plaque inflammation and detect macrophage-rich atheroma in preclinical studies, thereby enabling more comprehensive insights into atherosclerotic disease progression [77]. NIRF differs from NIRS in that it is much more versatile, depending on its molecular agent of choice and whether near-infrared autofluorescence is detected. NIRF-OCT and NIRF-IVUS Molecular Imaging The combination of both NIRF with OCT and IVUS opens many possibilities in coronary artery imaging due to the wide range of applicable NIRF agents. These agents can detect key biological processes, including plaque protease activity, macrophage infiltration, abnormal endothelial permeability, and fibrin deposition on stents. This flexibility allows both the target-

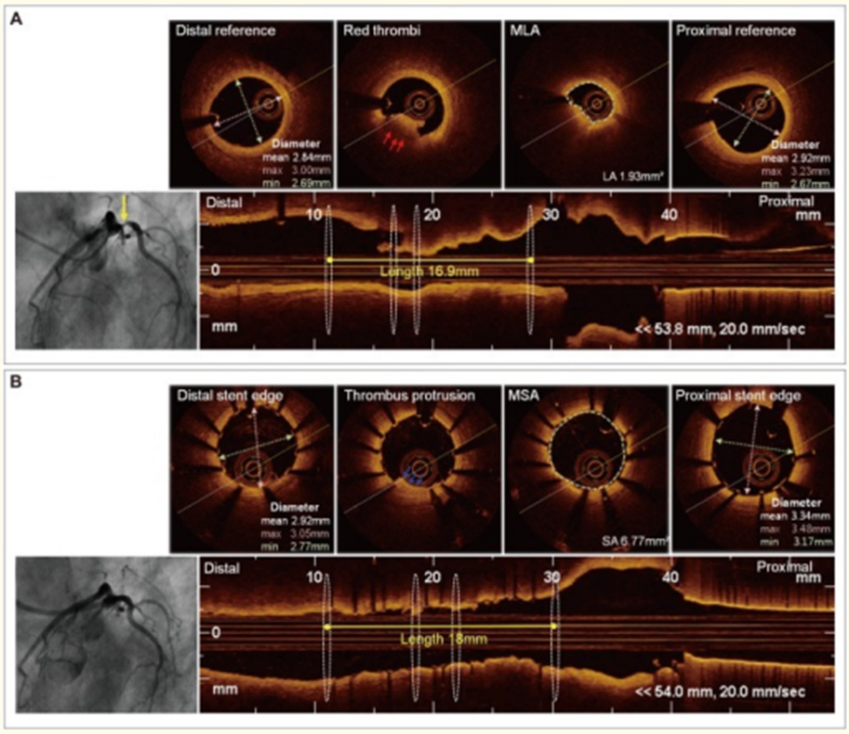

Figure 6: Angiographic and NIRS findings in acute STEMI patients. (A) Angiography of a patient with acute chest pain showing complete occlusion of the right coronary artery. (B) Aspiration image showing the characteristic thrombus of a STEMI patient. (C) After restoration of TIMI flow grade 3, NIRS revealed a circumferential lipid core plaque concentrated at the culprit site [86].

ing of specific molecular mechanisms involved in plaque vulnerability and the enhanced identification of high-risk plaques through NIRF-based imaging. NIRAF-OCT detection of IPH in CAD patients Intraplaque hemorrhage is a significant driver of plaque instability and progression in CAD, yet it was difficult to image clinically until recently [78,79]. More recently, a breakthrough in the form of a NIRAF-OCT imaging modality developed in collaboration succeeded in imaging coronary IPH in 12 patients [80]. NIRAF differs from NIRF in that no imaging agent is needed. Instead, it relies on the detection of endogenous autofluorescence in the plaque by resorting to blueshifted NIR light, e.g., 633-nm excitation vs. 750-nm excitation for NIRF. Mechanistic studies revealed that the origin of this autofluorescence is related to hemoglobin breakdown products, including bilirubin, associated with regions of IPH [80]. Such detection of IPH may be critical to the identification of plaques at increased risk for rupture and for targeted intervention.

In addition, more innovative combinations of imaging modalities have been explored to further improve outcomes in coronary assessments and interventions. Systems such as IVUS-OCT systems [8], fluorescence-IVUS-OCT [8], and NIRS-OCT [8] have been developed on the basis of their strengths. Their aim is for more comprehensive plaque characterization, detailed structural assessment, and molecular imaging in one procedure; thus, these hybrid systems will most likely be under extensive study in future clinical trials.

Conclusions

Several RCTs have shown the benefit of IVUS-guided PCI, with a reduction in MACE, primarily because of a reduction in TLR. Although the individual majority of trials revealed neutral effects on mortality and MI, the meta-analysis revealed a reduction in cardiovascular mortality and MI and stent thrombosis, particularly in

patients receiving newer generation drug-eluting stents and those with complex lesions. Patients with a clinical diagnosis of ACS or complex lesion types, such as left main, bifurcation, chronic total occlusions, and long lesions, who seem to derive the greatest benefit. A limitation of these studies is the heterogeneity of stent optimization protocols and the use of various imaging catheters of differing characteristics supplied by different vendors. Furthermore, imaging per se is not sufficient for outcome improvement-interpretation skills, and therapeutic responses should be appropriate, which, to a great extent, is operator dependent. Given such variability, the fact that IVUS-guided procedures yield positive outcomes despite many patients not reaching optimization targets indicates that vessel visualization and the intent of the operator to achieve optimal results greatly contribute to better outcomes. It remains unclear whether the mechanism of these benefits involves intermediate markers such as a larger minimum stent area or other factors. Further efforts are needed to standardize reporting protocols and optimize practical algorithms for lesion preparation, stent placement, and optimization, which need further study and comparisons. Integration of automated lumen, plaque, and stent segmentation and angiographic coregistration into imaging software may further help less experienced operators make accurate imaging-guided decisions. Given that IVUS guidance reduces TLR rates by approximately 50%, with minimal complications, and considering its well-documented cost-effectiveness, the current evidence strongly supports the use of IVUS in complex lesion subsets and potentially in all-comers. An identical strength of evidence is currently lacking for the remaining imaging modalities, including OCT and NIRS-IVUS. However, a series of ongoing clinical trials will provide further insight into how these emerging imaging tools might improve outcomes in patients undergoing percutaneous coronary intervention and in patients with CAD.

Declaration Statement

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