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Role of Intravascular Ultrasound and Optical Coherence Tomography in Intra Coronary Imaging for Coronary Artery Disease

Maruf Sarwar MD [1], Stephen Adedokun MD [2] and Mahesh Anantha Narayanan MD FACC [1,*]

[1] Department of Cardiovascular Sciences, White River Health, Batesville, AR
[2] Division of Cardiology, University of Tennessee at Memphis, TN
* Correspondence: manantha@umn.edu

Abstract: Coronary angiography, long considered the gold standard for coronary imaging, faces limitations in assessing coronary vessel wall anatomy and guiding percutaneous coronary intervention (PCI). Despite its prevalence, studies have demonstrated that it is suboptimal in estimating the severity of coronary disease and physiologic significance of stenosis. Intracoronary imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), offer promising alternatives to overcome these limitations. This review delves into the nuances of IVUS and OCT, highlighting their strengths and limitations as adjuncts to PCI. IVUS, utilizing ultrasound technology, and OCT, based on near-infrared light, each provide unique insights into coronary pathology. They differ in terms of temporal and spatial resolution, influencing their capabilities in plaque characterization and vessel assessment. The discussion navigates their historical evolution, technical specifications, and clinical utility. Meta-analyses and adjusted observational studies suggest that both IVUS and OCT-guided PCI correlate with reduced cardiovascular risks compared to angiographic guidance alone. While IVUS has demonstrated consistent benefits in terms of clinical outcomes, the evidence supporting OCT is less robust. However, the utilization of these imaging modalities remains variable across regions, with increasing adoption in recent years, particularly in IVUS-guided PCIs. Intravascular ultrasound's journey from early motion detection to current high-resolution mechanical systems is traced, including improvements in catheter size and compatibility. On the other hand, optical coherence tomography has advanced significantly, utilizing near infrared light to achieve unparalleled resolutions, albeit requiring temporary blood clearance for optimal imaging. In conclusion, IVUS and OCT offer valuable insights into coronary pathophysiology and guide interventions with improved precision compared to traditional angiography. While IVUS remains more extensively utilized, OCT's growing potential is underscored by advancements in technology, culminating in enhanced imaging capabilities. Both modalities demonstrate comparable clinical outcomes, emphasizing the need for tailored imaging choices based on individual clinical scenarios. The continued refinement and broader integration of intravascular imaging are expected to play a pivotal role in optimizing coronary interventions and patient outcomes.

Keywords: coronary artery disease; intravascular imaging; intravascular ultrasound; optical coherence tomography

Introduction:

Two-dimensional coronary angiography has been the gold standard for diagnostic and interventional coronary imaging, but it has got substantial limitations. Coronary angiography is limited in its ability to assess coronary vessel wall anatomy including luminal dimensions, plaque length, morphology, and to efficiently guide percutaneous coronary intervention (PCI) – e.g. assess for presence of dissections, stent apposition and expansion. Multiple studies have shown that even something as fundamental as estimating the severity of coronary disease is sub optimal with angiography - interventional cardiologists tend to overestimate degree of coronary stenosis before intervention[1] and underestimate after intervention. There is already extensive plaque in the vessel wall by the time the lumen gets compromised (Glagov phenomenon) on angiography and therefore is a major limitation while using angiography alone for decision making.[2] Furthermore, it is difficult to estimate the physiologic significance of a coronary artery stenosis by angiography alone - correlation between stenosis estimated on angiography and coronary physiology estimated by fractional flow reserve (FFR) is highly sub-optimal[3] and revascularization decisions made on the basis of coronary stenosis had inferior results in the FAME II study.[4] Visualizing stenosis with other modalities may overcome some of these limitations and intracoronary imaging might be one such option to improve decision making.[5]

In current day clinical practice, two major imaging modalities are being increasingly utilized for intra coronary imaging in patients with coronary artery disease (CAD) - intravascular ultrasound (IVUS) and optical coherence tomography (OCT). IVUS, as the name implies, is based on ultrasound properties, while OCT uses near-infrared light to generate an image. Both modalities carry their own advantages and limitations and so it is prudent to understand the nuances of different imaging technologies while choosing the right imaging technique to answer the question. For practical purposes, it is important to understand some of the crucial differences between the two techniques including differences in temporal and spatial resolution and the depth at which imaging is possible. This in fact influences the question that each technique can answer – plaque characterization vs. whole vessel characterization and how a stenosis is measured – lumen based in OCT vs. EEM based sizing in IVUS.

A general summary of the field seems to be that use of intravascular imaging guidance (IVUS or OCT) for PCI reduces the risk of cardiovascular death and major adverse cardiovascular events (MACE) when compared to angiographic guidance alone. The major evidence comes from meta-analyses of randomized clinical trials (RCTs) and adjusted observational studies but the effect was less robust in individual RCTs, primarily due to the limitations of the individual trials. Whereas it has been shown that IVUS guidance reduces the risks of all-cause death, myocardial infarction, target lesion revascularization and stent thrombosis, there is lesser evidence for OCT use in guiding PCIs. IVUS and OCT both seem to be comparable in terms of clinical outcomes.

How frequently do IVUS and OCT get utilized as an important adjunct to PCI remains unclear and there have been significant regional trends.[6] The National Inpatient Sample (NIS) database showed that these imaging modalities were used infrequently in the US (1.0% of all diagnostic angiography and 4.8% of all PCIs), but its use has been steadily increasing from 2.1% in 2004-2005 to almost 6.6% in 2013-2014. There appears to be a wide variability among the centers (Only 13% of facilities used intravascular imaging in >15% of PCIs) and many of them are IVUS guided PCIs (99%).

Intravascular ultrasound – Basic Background:

It was back in 1953 when Edler and Hertz recorded motion of cardiac structures[7] using M-Mode ultrasound. Yock et al developed a miniaturized model in 1991 for deploying a mechanically rotated device into an intravascular catheter. This paved way for rapid development of devices based on a mechanically rotated single element system or the phased array synthetic aperture system steered electronically.[8] These devices were further refined to have better speed and resolution. Mechanical systems had frequencies ranging between 20 to 40 MHz with an axial and lateral resolution of ~120 μm and 200 μm respectively.[9] Recently, 60 MHz mechanical devices are being used as they provide a higher resolution but are associated with an increase in blood speckle. This can affect optimal imaging and thus requires better filtering and image processing.[10] Device size has also been optimized and IVUS catheters can now be used with a 5 Fr guide catheter.

The use of IVUS imaging has significantly increased over the last decade, especially after the availability of data supporting its role in certain conditions. In some observational studies, IVUS has shown to improve clinical outcomes. However, there is wide variation in usage with a relatively higher use in the Far East when compared to some European centers including France.

The normal appearance of a coronary artery on IVUS depends on the ultrasound scatter from the different components in the arterial wall. Collagen reflects ultrasound the most and therefore the adventitia, with its high collagen, appears as a very bright structure. On the other hand, the external elastic lamina of the vessel (EEL), an important landmark for plaque measurement and vessel sizing, appears echo lucent. The intimal-medial layers affect ultrasound variably, and thus forming a part of the three-layered image. Atherosclerotic plaque typically starts as intimal thickening and then plaque

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growth obscures the differentiation of inner intimal-internal elastic lamina (IEL) from the media and so these two components are measured together as plaque volume in IVUS.

Optical Coherence Tomography – Basic Background:

Intravascular OCT uses light instead of ultrasound to image the artery and it currently is the most useable technique to obtain the highest resolution imaging of the coronaries. Current day OCT systems incorporate advanced near infrared light sources and optical components operating at a wavelength of 1310 nm and a low-coherence interferometer is used to measure the backscattered light. Tissue composition affects light reflection and propagation time for reflected energy and this is used to construct a 2-dimensional image of the optical scattering from tissue architecture. It originally started as a way to exquisitely image the retina and quickly evolved into multiple other applications including a catheter based form for vascular imaging.[11] The optical resolution of OCT is 10 times higher than that of IVUS (both longitudinal and temporal resolution).[12] A limitation of OCT is that it requires temporary clearance of blood from the imaging field as the penetration depth of OCT is only 0.5 to 2 mm and near infrared penetrates only for a short distance through blood.[13] Early systems thus required balloon occlusion, but modern systems accomplish clearance through simple flushing. The use of OCT has been slower than that of IVUS due to a number of reasons including cost, a longer learning curve and less robust data about its clinical advantage over IVUS. The introduction of frequency-domain OCT (FD-OCT) has enabled faster image acquisition, reducing motion artifacts and improving the overall efficiency of the procedure.[14, 15, 16] Moreover, the utilization of swept-source OCT (SS-OCT) has resulted in enhanced penetration depth and higher resolution, enabling detailed assessment of vessel layers and plaque morphology.[17, 18]

Methods:

The methodology for this review on IVUS and OCT guidance in coronary disease for patients with CKD and diabetes is based on the guidelines for evidence selection from the Journal of Clinical Medicine (JCM). The review aims to provide an in-depth evaluation of the safety and efficacy of IVUS and OCT in guiding coronary interventions in this specific patient population.

A comprehensive literature search was conducted through electronic databases, including PubMed, Embase, and the Cochrane Library. The search was performed up to July 2023 to ensure the most recent and relevant studies were included. The following keywords and medical subject headings (MeSH) terms were used in combination: "Intravenous Ultrasound," "IVUS," "Optical Coherence Tomography," "OCT," "coronary artery disease," "CAD," "diabetes mellitus," "diabetes," "coronary intervention," "percutaneous coronary intervention," "PCI," "intravascular imaging," "CKD," and "diabetic patients." The search was limited to studies published in English.

Studies were selected based on their relevance to the topic and adherence to the guidelines provided by Journal of Clinical Medicine. The inclusion criteria encompassed original research articles, randomized controlled trials, observational studies, systematic reviews, meta-analyses, and retrospective analyses. To ensure the focus on CKD patients with CAD and diabetic patients with CAD, studies that did not specifically address this patient population were excluded.

Data from selected studies were extracted and organized into a standardized format (Table 1), including study characteristics (e.g., authors, publication year), patient demographics, sample size, intervention details (IVUS or OCT), and clinical outcomes. The extracted data were then synthesized and analyzed to provide a comprehensive overview of the safety and efficacy of IVUS and OCT guidance in coronary interventions for patients with diabetes or CKD.

The objective of the quality assessment was to guarantee the reliability and validity of the evidence presented in this review. Every effort was made to include all relevant studies. As with any review, potential bias can exist in the selection and interpretation of studies, and the findings should be interpreted considering these limitations.

Are there advantages of using IVUS over plain Angiography?

There is significant evidence showing IVUS use during PCI has several advantages over using plain angiography to guide intervention – this is true with the older bare metal stents as well as the newer drug coated stents. Using IVUS guidance has changed both the soft and hard end points (MACE or stent thrombosis, etc.) even though the major benefit has been seen with the rate of restenosis and target vessel revascularization; RCTs, which have probably been underpowered, have not been consistent in showing benefit for hard end points, but evidence from collective studies like meta-analysis is very encouraging. Using IVUS may be very cost effective.[19] Who benefits the most is still an unresolved question but intravascular imaging is probably more beneficial in high risk patients and in those requiring complex interventions e.g. distal left main coronary artery (LMCA) lesions and patients with acute coronary syndromes (ACS).

Are there advantages of using OCT over plain Angiography?

Unlike IVUS, there is a scarcity of data comparing OCT vs. Angiography for optimizing PCI and all the available studies are either observational or registry based. There is data to suggest that OCT gives a better definition of PCI related complications and in detecting sub optimal stenting results (edge dissection, mal-apposition etc). There is also some evidence to suggest OCT allows better stent expansion.[20] But whether these outcomes have any meaningful major down-stream consequences remains unclear. It appears that use of OCT changes the clinical strategy in a significant number of subjects but whether this has any clinical implication is hard to prove.[21] One area of interest is to see if OCT guided intervention allows for better stent coverage and lowers neo atheroma which in turn could help predict the duration of DAPT. Early studies seem to suggest that this may be possible.[22] Finally, even if it does not show immediate benefits, intravascular imaging with OCT helps to understand the mechanism of stent failure and very late stent thrombosis.[23] It is probably reasonable to conclude that the bulk of the collective evidence would suggest that intravascular imaging has outcome advantages when compared to angiography.[5]

IVUS versus OCT: General Differences

While both IVUS and OCT provide vessel and plaque information, they differ in some important respects. One big difference in their clinical use is in vessel sizing – both modalities use different boundaries in a vessel for stent sizing. IVUS usually visualizes intima and EEL without being able to delineate the media and thus uses EEL for stent sizing while OCT uses the lumen edge for sizing. Kubo et al showed that for the same vessel in a phantom, IVUS overestimated vessel size by about 8% but OCT measurements were accurate.[24] The same was seen in a clinical study in which, mean minimum lumen diameter was lowest with QCA, while that by IVUS was larger than that measured by FD-OCT (2.09 ± 0.60 mm vs. 1.91 ± 0.69 mm; $p < 0.001$). The minimum lumen area behaved similarly and both imaging techniques were very reproducible, but OCT was still better. Automated OCT measurements are possible and are fairly accurate while those for IVUS readings often require human correction.[25] On the other hand, OCT has shorter depth penetration in imaging the vessel wall and lipid plaque can obscure any morphology behind it. Clinicians are more familiar with IVUS patterns and have used it for a longer period[2] while OCT requires a learning curve and has been in use for a much lesser time. While image patterns are being standardized,[10] there are still some grey areas like detecting macrophage infiltration, and this makes it difficult to have consistent definitions.[26] One limitation of IVUS is the vessel calcification (a reflector of ultrasound) and so it is challenging to obtain good images.[27] Recent studies show the importance of preparing a vessel bed in the face of extensive calcification in a vessel before stenting. This might be better with OCT since light travels through calcium with little backscatter unlike in lipid rich or necrotic core, which usually tend to produce signal poor regions with a diffuse border on OCT.[28] In chronic total occlusions, IVUS helps in both antegrade (resolves proximal cap ambiguity and facilitates reentry into true lumen from the sub intimal layer) and retrograde (reentry from false to true lumen) approaches but there is less data for OCT in this regard. One area where OCT will reign superior is estimating the cap thickness for

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thin cap fibroatheromas (TCFA) which is thought to be the sine qua non for a vulnerable plaque. A cap thickness of less than 65 microns is thought to denote a high-risk plaque and OCT is currently the best method to define this in vivo, provided careful quality control is established.[26]

How does OCT-guided intervention perform compared to IVUS-guided PCI?

OCT has better resolution, both lateral and axial, than IVUS and thus provides better imaging - it can thus be better for detecting dissections, mal-apposition, thrombus, neoatheroma and TCFA cap. On the other hand, IVUS can see farther out into the vessel (8 mm compared to about 2-3 mm for OCT) and is better for imaging larger vessels including LMCA ostium and calcified plaques. This led to great enthusiasm in exploring the appropriate imaging technique. Some early studies including RCTs have looked at this question, however, with somewhat disappointing results – the initial enthusiasm that the beautiful pictures obtained on OCT would translate into clinical superiority has not panned out as expected. The ILUMIEN II study did not find a difference in stent sizing between IVUS and OCT despite different approaches to sizing.[29] Two large RCTs are on the way (ILUMIEN-IV and OCTOBER trials) and might give us a better picture. The ILUMIEN-III study[30] showed no advantage of OCT-guided PCI over IVUS-guided PCI in stent size and expansion but showed lesser rates of mal-apposition. It was better than angiography-guided PCI as far as stent expansion and mal-apposition were concerned. Surprisingly, the incidence of dissection was similar to angiography guided PCI but less than with IVUS guided PCI. The other major RCT, however did not show major differences between the two forms of intravascular imaging[31] in terms of target vessel failure or stent size or rate of restenosis. In summary, OCT provides a better definition of procedural complications and shows sub optimal stent deployment better. This might help in detecting predictors of stent-related adverse events better than with IVUS. It appears that under-expansion and edge disease remain major predictors of suboptimal outcomes with both techniques. Better detection of acute stent mal-apposition with OCT does not seem to have any advantage over IVUS in predicting or averting early or late restenosis or thrombosis.

Safety with IVUS and OCT

Intravascular images are obtained in both techniques after engaging the coronary ostium with the guiding catheter and insertion of a guidewire, which is then followed by the insertion of IVUS or OCT catheter over the wire. There are a few complications associated with using both IVUS and OCT, with higher rates of complications with ACS compared to non ACS patients with stable angina pectoris and in asymptomatic patients (2.1% in ACS compared to 0.8% and 0.4% in stable angina and asymptomatic patients).[32] Like any other intravascular procedure, these catheters require use of anticoagulation with heparin. Nitroglycerine is routinely administered considering 3% reported incidence of coronary spasm associated with these imaging techniques.[32,33] Complications other than the spasms include embolism, dissection, acute vessel occlusion, thrombus formation and usually present as acute myocardial infarction or requiring emergency coronary artery bypass surgery. In the IUVS PROSPECT trial which included 697 ACS patients receiving three-vessel coronary imaging, complication rate was 1.6% including 10 dissections and 1 perforation.[33,34] In the more recent Thoraxcenter study from Rotterdam, NL, in which 1000 OCTs and 2500 IVUS were performed, the complication rates were much lower with no difference between the two imaging modalities and with no major adverse cardiac events.[35] As with any procedure, the complications are lowest in centers using this on a regular basis than those doing fewer studies.

IVUS enables precise measurements of the vessel size and plaque burden, as it can penetrate to the adventitia, including the external elastic membrane. This facilitates mid-wall or true vessel stent sizing, optimizing stent dimensions, and identifying areas with the smallest plaque burden to minimize geographical miss. Proper stent positioning and expansion are crucial factors in reducing the incidence of restenosis and stent thrombosis, both of which can have significant long-term implications for patients.[36] IVUS has established predictors of stent failure, such as stent underexpansion, major edge dissections, and geographical miss.

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Several meta-analyses have confirmed the benefits of IVUS guidance. One meta-analysis of randomized trials comparing IVUS-guided bare metal stent implantation with angiography-guided procedures revealed a reduction in restenosis and repeat revascularization, without impacting death or myocardial infarction.[37] Two recent meta-analyses of studies comparing IVUS-guided drug-eluting stent procedures with angiography-guided interventions showed a decreased incidence of death, major adverse cardiac events, and stent thrombosis.[38, 39] These findings are supported by additional clinical studies, including the RESET trial from South Korea and the ADAPT-DES observational study involving over 8,500 patients.[40, 41] Collectively, these advantages demonstrate the significant role of IVUS in improving outcomes and safety in coronary interventions.

Some Clinical Uses of intravascular imaging

Stenosis severity: Left main coronary artery lesions

Assessment of the LMCA with angiography can be challenging. IVUS of LMCA has been shown to correlate more with FFR measurement of the LMCA.[42] It is important to remember the difference in LMCA sizes between the various ethnic groups. In general, Asian population have a smaller vessel diameter, and so MLA when compared to the western population. In Koreans, an IVUS LMCA MLA of 4.5-5.8 mm2 results in negative FFR (FFR≥0.8) while in the western population, LMCA MLA of less than 6 mm2 has been shown to be associated with an FFR of <0.75.[42] In a Spanish registry,[43] patients with an MLA>6 mm2 (179/186), who did not get revascularization, had similar cardiac death free survival (p=0.5) when compared to patients who had MLA < 6 mm2 (152/168) and who had revascularization. Also, even free survival in both the groups were similar (P=0.3). The study also showed that people who had MLA between 5 to 6 mm2 did worse when treated only with medical therapy without revascularization. In a study of 122 patients with LMCA lesion not treated at the time of IVUS assessment, the annual event rate was about 14% and minimal luminal diameter on IVUS was the most important predictor of cardiovascular events.[44] Ideally, IVUS should be done from both the left anterior descending and left circumflex artery to evaluate LMCA dimensions. OCT has got a few limitations including the requirement of contrast and inability to measure ostial lesions. But OCT is ideal to measure distal left main lesions which is prone to form complex plaques extending left anterior descending and left circumflex arteries.[45]

Stenosis severity: Non-Left main coronary artery lesions

In non-LMCA lesions, MLA of 4 mm2 has been shown as the cut off to differentiate between vessels with and without ischemia. In a study by Abizaid et al, MLA>4 mm2 was found to be associated with a coronary reserve of ≥2.[46] When revascularization was deferred based on MLA > 4 mm2, IVUS MLA and area stenosis (AS) were the only independent predictors of MACE at follow up.[47] FFR is known to be the gold standard for evaluation of ischemia in three randomized controlled trials (RCTs) and FFR based revascularization for patients with a value of <0.8 has been shown to improve patient outcomes and prognosis.[4,48-51] Comparison between FFR and IVUS in patients with intermediate coronary lesions was performed in a recent study.[52] FFR of <0.8 and MLA on IVUS <4 mm2 were used as criteria for revascularization. 94 lesions were treated with IVUS whereas 83 were treated with FFR. A significant number of people in the IVUS arm underwent revascularization therapy when compared to FFR guided therapy (92% and 34% respectively, P<0.001) but there was no significant difference in MACE at 1 year follow up (3.6% in FFR guided PCI versus 3.2% in IVUS guided PCI). In a few published studies, the range of IVUS measurements guiding ischemia ranged from 2.1 mm2 to 4.4 mm2 suggesting inconsistency. One needs to be aware of the difference in vessel dimensions between the western population (higher MLA) and the Asian population (typically lower MLA) while interpreting IVUS MLA. The sensitivity of IVUS MLA (<4 mm2) compared to FFR was only 92% with a 56% specificity, while a longer lesion length of >10 mm had a sensitivity of only 41% with higher specificity of 80%.[53] Based on the various studies, it can be concluded that an IVUS MLA of >4 mm2 could be treated conservatively (higher negative predictive value) but treating all lesions <4 mm2 MLA on IVUS leads to treating almost 50% of lesions without ischemia (lower positive predictive value).

There is a good correlation between IVUS and OCT measured MLA with nearly similar sensitivity and specificity.[54] OCT guided MLAs are typically smaller in the range of 1.6 mm2 to 2.4 mm2. In an OCT based study treating 62 intermediate lesions in 59 patients, an OCT derived MLA of <1.91 mm2 and percentage lumen AS of > 70% were shown to correlate well with an FFR of <0.75. OCT suffers similar limitations like IVUS with a higher negative predictive value but a lower positive predictive value. There are no RCTs comparing IVUS to OCT similar to FFR and iFR studies. It is important to remember that both IVUS and OCT, do not take into account, the subtended viable myocardial mass, or information on antegrade or retrograde flow through collaterals.

Monitoring Plaque Morphology and Changes with Therapy:

A number of studies were done to evaluate the effect of medical therapy on plaque volumes and IVUS has been the preferred mode of imaging in most of these studies. This has helped us understand plaque biology and effect of treatments including statins and more recently, the PCSK-9 inhibitors (Puri JAMA Cardiology 2018). For example, Von Birglelen et al followed mild LMCA atherosclerosis over a period of 18±9 months and showed that LDL levels correlated with plaque progression whereas HDL levels had an inverse correlation.[55] The REVERSAL (Reversal of atherosclerosis with aggressive lipid lowering) is a double blinded RCT that demonstrated IVUS derived atheroma volume showed a significantly lower progression of atherosclerotic plaque in patients treated with atorvastatin (P=0.02).[56] Progression of plaque did not occur in the atorvastatin group whereas the pravastatin group had plaque progression. The ESTABLISH trial also showed regression of plaque volume in the atorvastatin group.[57] In ASTEROID, the mean percentage atheroma volume (PAV), the most reliable IVUS measure of disease progression and regression, showed significant regression in patients treated with high dose rosuvastatin.[58] However, it is essential to standardize the methods for plaque assessment, and this in fact comes with significant challenges.

Some would argue that it is important to identify vulnerable plaques, but this view is controversial.[59] The most common finding of the so-called vulnerable plaque is the TCFA, a precursor for thrombotic plaque rupture. Greyscale IVUS has suggested four different morphologies consistent with a TCFA including large plaque burden, shallow echolucent zones, spotty calcifications and attenuated plaque (shadowing without calcification) though only the former three (except attenuated plaque) have been shown to be associated with adverse outcomes including myocardial infarction, hospital admission and need for PCI.[34, 60, 61] The largest data comes from the virtual histology IVUS that has shown to predict future adverse events in non-culprit lesions. Both grey scale IVUS and radiofrequency (RF) IVUS (integrated backscatter IVUS and virtual history IVUS) have shown to predict cardiac events. The difference between OCT and radiofrequency IVUS is that RF IVUS can only suggest the presence of TCFA by identifying the necrotic core along the lumen whereas OCT is able to define the thickness of a thin fibrous cap less than 65 μm, macrophages in the fibrous cap and also presence of underlying lipid core. Studies have shown that the presence of a higher plaque burden of >70% can be used to predict a TCFA, able to differentiate between ruptured and non-ruptured atheroma and to identify the culprit versus non-culprit plaque ruptures. Another OCT based study showed that the rapid angiographic lumen loss of >0.4 mm in 7 months was associated with increased frequency of intimal laceration, micro-vessels, TCFA, macrophages, lipid accumulation and intraluminal thrombi.[62] There are a few other studies evaluating using the NIRS technique to identify vulnerable plaques, including the LRP (NCT02033694), PREDICT (NCT02792075), and PROSPECT-2 (NCT02171065) trials.

Serial intravascular imaging has shown that plaque morphology could rapidly change over a period of few months without actual rupture, especially in patients treated with high dose statins. As intravascular imaging is invasive, it is important to evaluate the appropriateness of imaging to identify vulnerable plaques, which again depends on the prevalence of TCFAs, their frequency, stability, pharmacotherapy needed during the procedure and complications associated with intravascular imaging. It is essential to understand that there are a lot of grey areas in this space – we don't have a

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consistent technique or definition that best predicts outcomes in vulnerable plaques - studies have shown wide disagreement between the different imaging modalities, including grey scale IVUS, RF IVUS, angioscopy, OCT and NIRS, often in the range of 25-30%. These techniques suffer from biased populations and high sensitivity at the expense of low specificity.[34]

Patients with Chronic Kidney Disease (CKD)

Conventional PCIs often lead to severe complications in patients with CKD. However, both low-to-zero contrast IVUS and low molecular weight dextran (LMWD) OCT-guided PCIs offer a promising alternative for CKD patients. Minimal contrast and contrast-free IVUS-guided procedures demonstrate safety in both cardiac and renal outcomes, comparable to conventional PCIs, even for complex atherosclerotic lesions. The OCT intravascular imaging modality offers a higher axial resolution than IVUS, but its increased use of contrast volume is linked to contrast-induced nephropathy (CIN) development. Zero and LMWD contrast OCT-guided PCI produces safe, effective outcomes comparable to both traditional intervention and IVUS-guided PCI.

Burlacu, et al performed a systematic review to include studies evaluating the efficacy and safety of PCI using IVUS and minimal or zero-contrast in chronic kidney disease patients.[63] Of the 238 patients, none of the patients in the studies experienced renal function deterioration or required renal replacement therapy following the zero-contrast IVUS-guided procedures. Moreover, from a cardiovascular standpoint, this technique has proven to be safe with favorable cardiovascular outcomes.[63, 64, 65, 66, 67, 68, 69]

The CONSaVE-AKI study was a prospective, randomized study that assessed short-term outcomes and safety of ULC-PCI compared to conventional PCI in patients with ACS who were at high risk for contrast induced acute kidney injury (CI-AKI). Patients who had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 with a moderate to very high Maioli score for pre-procedural risk of developing CI-AKI were included in the study. All patients (n=82) were randomized and equally divided into two equal groups: ULC-PCI and conventional PCI. IVUS was used in 17% of patients within the UCL-PCI group. The development of CI-AKI, occurred significantly more in patients who underwent conventional PCI (17.1%) than in the ULC-PCI group (0%), (p = 0.012). Contrast volume was also significantly lower in the ULC-PCI group (41.02 ±9.8 ml vs 112.54 ±25.18 ml; P < 0.0001). The use of IVUS guided imaging helped to reduce the contrast utilization drastically and to effectively reduce the incidence of CI-AKI. Intervention by ULC-PCI with IVUS guidance is feasible and can be safely used in patients with renal dysfunction to reduce the incidence of CI-AKI.[70]

Sakai, et al examined the use of IVUS-guided minimum-contrast (MINICON) PCI (n=98) compared to standard angiography-guided PCI (n=86) in patients with advanced CKD (n total= 184). The IVUS-guided MINICON PCI group showed significantly reduced contrast volume and a lower incidence of CI-AKI compared to the angiography-guided standard PCI group (CI-AKI; 2% vs. 15%; P = 0.001). The success rate of the PCI procedure was similarly high in both groups (100% vs. 99%; P = 0.35). At the one-year follow-up, the IVUS-guided MINICON PCI group had a lower rate of renal replacement therapy (RRT) induction (RRT; 2.7% vs. 13.6%; P = 0.01), but there were no significant differences in all-cause mortality or myocardial infarction between the groups.[64] These findings suggest that IVUS-guided MINICON PCI produce high success rates and effectively reduce CI-AKI and RRT induction in patients with advanced CKD.

Sacha, et al performed a retrospective analysis on the safety and efficacy of zero-contrast IVUS PCI in patients with severe renal impairment and hemodialysis subjects. Zero-contrast IVUS PCI was performed within 29 coronary arteries in 20 patients with advanced CKD. This group included four patients who were treated with hemodialysis but presented preserved residual renal function. The estimated median probability of AKI in non-dialysis patients undergoing standard PCI using 100-200 ml of contrast medium was 57%. This median risk estimation reduced to 26% when using the assumption that contrast dye was not used. With the zero-contrast IVUS approach, the factual risk of AKI was reduced to 10% and no patient required renal replacement therapy. The technique also yielded good clinical outcomes in mid-term observations. During the median follow-up of 3.2 (1.2–5.3) months no patient experienced an acute coronary event or required revascularization. IVUS identified the lesion length, determined balloon and stent diameters, and landing zones for stent implantation, as well as verified and documented the final PCI effect. Since the procedure was based on IVUS imaging, it allowed optimization of stent implantation with good procedural results, and consequently no stent thrombosis occurred during the follow-up.[65] The study's results indicate if the patient is at a high risk of AKI, zero-contrast-IVUS PCI should be considered as a preventative solution, even for dialysis patients with residual renal function.

Kumar, et al sought to assess the safety and short-term outcomes of 'absolute' zero-contrast PCI under IVUS guidance in CKD patients. There were 42 CKD patients who underwent absolute zero-contrast PCI under IVUS guidance. A total of 66 coronary vessels underwent intervention, including 14 (21.2%) LMCA PCI (seven of which were LMCA bifurcation PCI) and three chronic total occlusion (CTO) PCI procedures. Even with the inclusion of these complex PCIs, technical success was 92.4% without any major complications. Two patients died of non-cardiac causes on follow up (3–12 months), and all the remaining were symptom free.[67] IVUS-guided 'absolute' zero-contrast PCI is feasible and safe for CKD patients, allowing successful completion of the procedure without any contrast or complications, even in complex lesion morphologies.

Ultra-low contrast PCI guided by zero-contrast OCT can be safely performed without major adverse events in non-STEMI patients with high-risk CKD who require revascularization. Liu, et al evaluated the safety and efficacy of zero contrast OCT-guided PCI in CKD patients with NSTEMI. The study involved 29 NSTEMI patients with high-risk CKD (median Cr = 2.1) undergoing revascularization. There were no significant changes in creatinine level or eGFR in the short- or long-term. OCT's high-resolution imaging capabilities enabled precise assessment of coronary lesions and better guided interventional procedures with greater accuracy. During the PCI procedure, OCT revealed 15 (52%) cases of abnormalities post-dilation. The main approach, zero-contrast OCT, resulted in safe and successful PCI without AKI, CIN, and the need for renal replace therapy. Furthermore, no patients experienced post-interventional complications and no MACEs were observed.[71]

Azzalini, et al also reported that it is feasible to use dextran as a substitute for contrast in OCT guidance. The study evaluated the feasibility of an ultra-low contrast volume percutaneous coronary intervention (ULC-PCI) protocol in patients with severe CKD. Extensive intravascular dextran-based OCT guidance was used to compare the outcomes of the ULC-PCI protocol vs conventional angiography-based PCI in patients with eGFR <30 mL/min/1.73 m^2. Technical success was achieved in all ULC-PCI procedures, and the incidence of CI-AKI was 0% vs 15.5% in the ULC-PCI and conventional groups, respectively ($P = 0.28$).[72] The implementation of an ULC-PCI protocol with OCT guidance in patients with advanced CKD is both achievable and safe. Furthermore, this approach shows promise in reducing the occurrence of CI-AKI when compared to the conventional angiographic guidance used alone.

Though OCT's 10-fold higher axial resolution than IVUS allows precise plaque and lumen characterization, its contrast flushing requirement increases total volume used, risking contrast-induced nephropathy. Kurogi et. al evaluated OCT-guided PCI using LMWD in patients with CKD. This single-center retrospective study found that OCT-guided PCI using LMWD as a flushing medium did not negatively affect renal function compared to IVUS-guided PCI using contrast media alone. There were no significant differences between 133 matched pairs of OCT and IVUS patients in changes in serum creatinine or eGFR after the procedure. The incidence of contrast-induced nephropathy was also similar between groups (1.5% OCT vs 2.3% IVUS). When stratified by CKD stage, there were again no differences between OCT with LMWD and IVUS with contrast in renal function changes or contrast volumes used. The study suggests OCT imaging with LMWD is a feasible approach that does not impair renal function relative to IVUS imaging with contrast alone, supporting its use as an alternative flushing medium in patients with CKD undergoing PCI.[73]

Recently, saline has been explored as a replacement for contrast to primarily avoid nephrotoxicity risks and expand FD-OCT to more patients safely. Several studies have aimed to evaluate if saline could provide adequate image quality in coronary FD-OCT.[74,75] The SOCT-PCI study demonstrated the feasibility of using heparinized saline as a flushing medium for FD-OCT image acquisition during PCI optimization. In 27 patients undergoing FD-OCT-guided PCI, heparinized saline was used for blood clearance during 118 OCT runs. Overall, 61% of runs were good quality, 27% were clinically usable, and 88% were clinically effective for PCI optimization. There were no significant hemodynamic or arrhythmic changes. Saline FD-OCT enabled visualization of coronary lesions and post-PCI optimization comparably to contrast FD-OCT in one case.[74] This suggests saline could replace contrast as the flushing medium for FD-OCT during PCI in patients at risk of contrast-induced nephropathy.

Gupta et. al explored saline as an alternative to radio-contrast for OCT-guided PCI. This prospective study analyzed 13 pairs of OCT runs using both contrast and heparinized saline in the same coronary arteries during PCI. The primary endpoints were quantitative measurements of minimal lumen area, reference diameters, and area stenosis. There were no significant differences in these primary endpoints between saline and contrast OCT. Bland-Altman analysis demonstrated good agreement without proportional bias between the two-flushing media for vessel measurements. All plaque morphologies and post-PCI optimization parameters were clearly visualized in the saline runs similar to contrast. The results indicate heparinized saline can yield comparable dimensional measurements and adequate image quality versus contrast for coronary OCT during PCI optimization. Using saline could not only eliminate the risk of contrast-induced nephropathy, but also produce high quality images in high risk patients.[75] While both of these studies show promising results for the use of saline in OCT, further large scale randomized studies directly comparing saline and contrast OCT are still needed to validate these findings.

Patients with Diabetes Mellitus

CAD remains a significant health concern, particularly in patients with diabetes mellitus, who often present with more complex and diffuse lesions. It has been previously demonstrated that coronary remodeling enables patients to develop large atherosclerotic plaques without a reduction in lumen size, leaving diabetic patients at high risk for developing myocardial infarction.[2] IVUS guidance during PCI has emerged as a valuable tool in optimizing outcomes for these high-risk patients. IVUS revealed that the prevalence of asymptomatic CAD in T2D patients is high, suggesting a need for a broader residual CV risk management using alternative approaches.[76]

Numerous studies have reported the benefits of IVUS guidance in diabetic patients undergoing coronary interventions. The ABCD trial is the first trial to date to perform invasive IVUS imaging, a gold-standard technique for evaluation of CAD, in asymptomatic patients with T2DM and revealed a CAD prevalence of 84%, indicating a significantly higher burden of disease than previously assumed.[76, 77] IVUS provides accurate measurements of coronary vessels, enabling precise stent sizing and better stent deployment. Specific coronary lesions associated with diabetes are mainly confined to coronary small-vessels. IVUS allows physicians to analyze and diagnose small-vessel lesions to improve the therapeutic effect of available interventional approaches more accurately. Arora, et. al demonstrated that the addition of IVUS guidance was associated with larger post-PCI minimum lumen diameter and more post-dilatation, which translated into clinically and statistically significant lower rates of target lesion revascularization or in-stent restenosis after drug eluting stent (DES) implantation.[76] By characterizing plaque morphology, IVUS helps identify vulnerable lesions, leading to a more tailored and effective treatment approach.

Regarding safety, the reviewed studies generally reported no significant increase in adverse events associated with IVUS-guided PCI in diabetic patients. Rahman, et. al's retrospective observational study demonstrated a significant reduction in MACE in diabetic patients (n = 73/134, 54.5%) who underwent IVUS-guided PCI. MACEs occurred in 9.7% of patients, where 3% of patients experienced heart failure. Furthermore, iatrogenic coronary dissection was zero.[78] The use of IVUS resulted in a significant decrease in MACE. IVUS appeared to contribute to a reduction in procedural complications, such as stent thrombosis and restenosis.

The precise stent placement achieved with IVUS may contribute to improved long-term patency and decreased incidence of adverse events. These findings underscore the potential long-term benefits and procedural safety of IVUS guidance in this high-risk population.

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Conclusions

In conclusion, intravascular imaging, specifically IVUS and OCT, has demonstrated significant benefits in accurately assessing vessel dimensions, plaque burden, and vulnerable lesions. IVUS is valuable in guiding optimal stent sizing and positioning, leading to improved procedural outcomes and long-term patient benefits. It also offers a low contrast usage advantage, reducing the risk of CI-AKI in CKD patients. On the other hand, OCT's high-resolution imaging allows for detailed visualization of coronary arteries, aiding in precise stent positioning and identifying vulnerable plaques. Both modalities have their unique strengths, and their use may depend on patient characteristics and lesion complexities.

Despite the proven benefits, the adoption of intravascular imaging has been limited, partly due to the reliance on collated studies and underpowered RCTs for hard clinical outcomes. Cost and a steep learning curve are also contributing factors. However, increasing use is observed in complex lesions and high-risk patients, and advancements in technology such as heartbeat OCT, high frame IVUS, and automated analysis are expected to further promote its incorporation into clinical practice. Well-conducted RCTs may be necessary to determine the appropriate use of these techniques.

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