

The Role of Intravascular Ultrasound in the Endovascular Treatment of Femoropopliteal Artery Lesions

How IVUS can be used to collect and analyze data on vessel and lesion characteristics to influence the success of femoropopliteal treatment.

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Intravascular ultrasound (IVUS) uses a transducer or probe attached to a catheter to generate ultrasound waves and provide a 360° cross-sectional view of blood vessels.¹ This modality produces key information regarding vessel and lesion characteristics and is a promising tool for improving the quality of endovascular treatments (EVTs).²⁻⁶ Recent studies have shown the utility of IVUS in percutaneous coronary intervention.⁷⁻⁹ However, the evidence regarding its clinical impact for peripheral artery disease (PAD) therapies remains limited, particularly for challenging femoropopliteal (FP) artery lesions.

WHAT DOES IVUS TELL US?

In FP intervention, IVUS can provide accurate vessel diameter measurements and details of plaque characteristics, including calcification severity, which strongly influences decision-making regarding treatment strategy,

technical approach, and long-term success. Accurate understanding of vessel morphology enables appropriate selection of device types and sizes, as well as determining a vessel preparation methodology for bridging to a final device (eg, drug-coated balloon [DCB], drug-eluting stent [DES], stent graft [SG]).

Vessel Diameter Evaluation

In principle, the standard method for angiography-measured vessel diameter has been lumen-based, whereas IVUS evaluation of vessel diameter is external elastic membrane (EEM)-based (Figure 1). Appropriately assessing vessel diameter is clinically important in device selection and sizing because using a larger device, if appropriate, will provide better long-term patency (Figure 2). In general, in device selection, the size of the SG is selected based on lumen evaluation, whereas the DCB and DES are sized 1:1 based on EEM evaluation.

Plaque Characteristics, Including Calcification Severity

Calcification severity influences post-EVT outcomes. In particular, circumferential calcification adversely affects primary patency after bare-metal stent (BMS), DES, and DCB treatment.¹⁰⁻¹² In the field of coronary intervention, the presence of deep calcification is also reported as negatively affecting the ability to achieve good patency.¹³ Given this, more precise assessment of calcification severity should be performed, particularly because this may guide treatment strategies, including up-front use of atherectomy. IVUS plays an important role in detailing the degree and severity of calcification. Figure 3 shows representative cases complicated by vessel calcification,

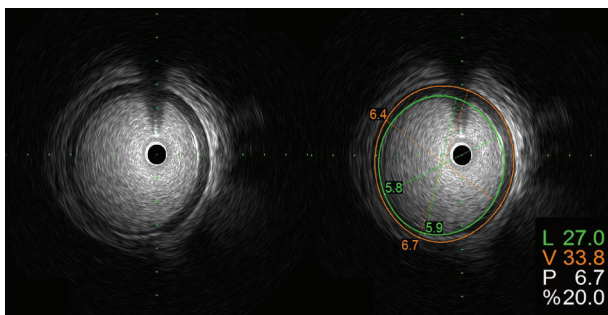


Figure 1. Vessel diameter assessment by IVUS. Precisely assessing vessel diameter by IVUS is generally based on EEM. This normal-looking vessel represents a 6.4-mm short axis by a 6.7-mm long axis.

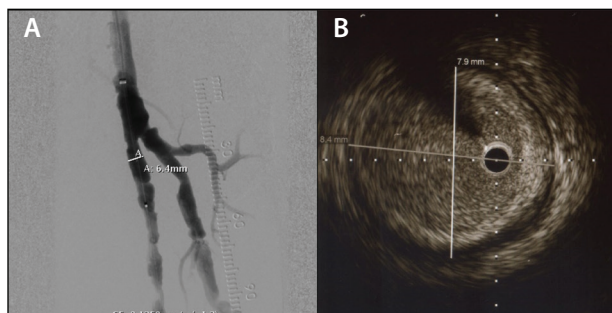


Figure 2. Assessment of vessel diameter by lumen-based angiography (A) versus EEM-based IVUS (B). When we assess vessel diameter by angiography versus IVUS, the different assessment tools lead to different device sizing, which can consequently impact long-term results.

which is seen in the white portion of the top row (the real IVUS images) and the gray portion of the bottom row. When these images are detected by IVUS evaluation, adjunctive therapy in addition to a conventional approach are considered to achieve technical and long-term success.

After successful wire crossing in the endovascular procedure, especially if the lesion is complicated by the presence of calcification $> 180^\circ$, adjunctive therapy using either ablation with an atherectomy device, pressure-oriented angioplasty with a noncompliant balloon, or plaque modification with a scoring or lithotripsy balloon should be considered to achieve sufficient acute gain. After confirming gain or dilatation in IVUS assessment, the lesion can subsequently undergo treatment with a primary therapy device (BMS, DCB, DES, SG).

The 12-month patency rates for these devices are generally better among the Japanese population than in patients in other countries.¹⁴⁻¹⁷ An explanation for these better results remains unclear, but one possible reason is that selecting an appropriate device size and placing the device in an appropriate location in conjunction with IVUS may contribute to better results.

Another role of IVUS application is to predict long-term success based on poststent expansion evaluated by IVUS. Similar to coronary intervention,¹⁸ the literature has reported that poststent expansion, namely minimum stent area, was significantly associated with loss of patency after stent-based treatment.^{3,19} There has been a tacit understanding that self-expanding stents have the ability to gradually and automatically reach each stent size without aggressive postdilatation; these results indicate that aggressive postdilatation for achieving a larger minimum stent area would guarantee better long-term success and reiterate the important role of postdilatation.

Superficial calcification		Deep calcification	
$<180^\circ$	$\geq 180^\circ$	$<180^\circ$	$\geq 180^\circ$

Figure 3. The severity of calcification according to location (superficial vs deep) and angle ($< 180^\circ$ vs $\geq 180^\circ$).

CAN IVUS IDENTIFY FACTORS INFLUENCING TECHNICAL/LONG-TERM SUCCESS IN FP LESION TREATMENT?

Various studies have examined the predictors of technical and long-term success in the EVT of FP lesions. Technical success of the endovascular procedure is generally defined as residual stenosis $< 30\%$, absence of severe vessel dissection, and a mean pressure gradient < 10 mm Hg. In clinical practice, residual stenosis is more important in determining technical success than severe vessel dissection or pressure gradient, and there is a need to predict which lesions will likely have a higher residual stenosis to develop a treatment strategy. In this regard, a subanalysis comparing stented versus nonstented lesions using the data from the IN.PACT Global registry identified representative characteristics related to DCB failure.²⁰ In the DCB with provisional stenting group, lesion length was greater, the frequency of chronic total occlusion (CTO) and severe calcification was higher, and the percent diameter stenosis was higher, demonstrating that adjunctive therapies such as atherectomy or stenting will be needed to achieve technical success. Based on this scenario, to maximize the performance of the final device and predict consequences after angioplasty (unfavorable lesions receiving balloon-based treatment only), IVUS should play a more important role in the detailed evaluation of lesion morphology pre- and postintervention.

On the other hand, there are also reports on predicting long-term success after treatment using devices of various generations. We proposed the utility of a classification based on clinical and lesion-related factors after BMS implantation in FP lesions. In this model, six items were included in the classification, which we referred to as the FeDCLIP score: female sex, diabetes, dialysis, critical limb ischemia (CLI), lesion length > 150 mm, and poor

runoff.²¹ The FeDCLIP score is able to stratify 5-year primary patency after BMS implantation. As we move from the classical BMS era to the next generation of antirestenotic devices, more attention is being paid to the evaluation of vessel characteristics. In our ZEPHYR study evaluating the outcomes of Zilver PTX DESs (Cook Medical) in real-world FP lesions, patient clinical characteristics were not identified as factors predicting restenosis. However, lesion length, distal vessel diameter, and minimum stent diameter were identified as associated factors.¹⁹

Earlier this year, we reported the results of the IVORY study, which evaluated endovascular outcomes in combination with IVUS evaluation and found that lesion length, distal vessel diameter, and presence of CTO were significant prognostic factors for 1-year restenosis.²² Also in the IVORY study, contrary to risk stratification using the FeDCLIP model, female sex, CLI, and poor runoff were not significantly associated with 1-year restenosis. Why are these variables traditionally reported as predictors of restenosis? Closely assessing these traditional variables (female sex, CLI, poor runoff), we found that female patients have smaller vessel diameters and longer lesions than male patients; patients with CLI have smaller vessel diameters, longer lesions, and more frequent CTOs than patients without CLI; and patients with poor runoff have smaller vessel diameters than those without poor runoff. These results suggest that systemic factors may be related to anatomic factors. Thus, as with achieving technical success, there is a need for a detailed treatment plan with IVUS investigating lesion length, distal vessel diameter, and complete occlusion, as shown in the IVORY study.

PROCEDURAL STEPS UNDER IVUS EVALUATION: “LEAVE NOTHING BEHIND” VERSUS “LEAVE SCAFFOLDING BEHIND”

In Japan, peripheral intervention of calcified lesions is impractical. First, no atherectomy devices are available for peripheral interventions. Second, bailout BMS implantation after DCB failure in the initial procedure is not covered by Japanese insurance. Given this unique situation, it is

critical to ensure that a lesion can be treated completely using DCB alone. In general, the presence and severity of vessel calcification is the main driving factor for deciding between a “leave nothing behind,” DCB-based strategy or a “leave scaffolding behind” stent-based strategy. Lesions that cannot be treated completely using DCB alone should primarily be considered for stent treatment. In other words, stenting is almost always used for CTO lesions and calcified lesions that are expected to recoil, regardless of stenosis or occlusion. When treating CTO or calcified lesions, the degree of gain obtained with predilatation determines the long-term outcome of the device to place afterward.

Case 1: “Leave Nothing Behind” Under IVUS Evaluation

An example of a case treated with DCB under IVUS evaluation can be seen in Figure 4A.

Step 1. From the initial angiogram, broadly identify the lesion length, vessel diameter, calcification severity,

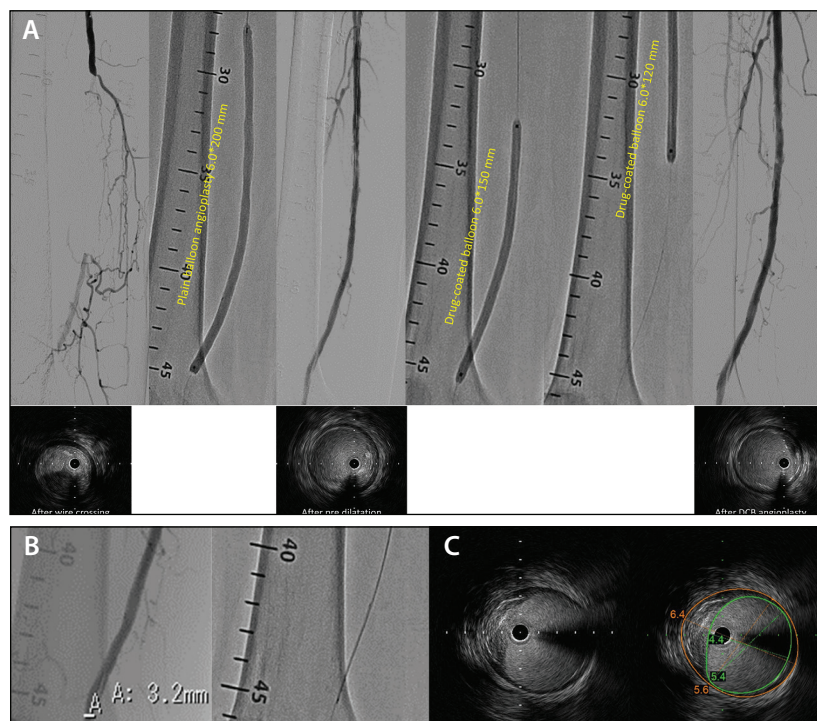


Figure 4. A representative case of DCB treatment under IVUS evaluation. Angiographic scenario of DCB treatment under IVUS evaluation (A). There is a big discrepancy of vessel diameter between angiography (lumen-based) versus IVUS (EEM-based) assessment. Here, the vessel diameter assessed by angiography is 3.4 mm, representing an indication for 4-mm balloon use for balloon dilatation (B). However, the vessel diameter assessed by IVUS is 6.4 X 5.6 mm, representing an indication of 6-mm balloon use (C). Differential modality would lead to a different size of device selection.

and distal/proximal healthy reference location.

Step 2. Determine the distal landing position of the DCB and evaluate the vessel diameter in that area. In general, there is a big discrepancy in vessel diameter between the angiography (lumen-based) assessment and the IVUS (EEM-based) assessment (Figure 4B).

Step 3. Subsequently, pull back the IVUS catheter and evaluate the entire vessel. Calcification severity is also evaluated at this time.

Step 4. As a rule, predilatation should generally be considered when selecting a balloon, which should not cause severe dissection but still provide the most gain. However, in recent years, we've seen balloon size selection for the distal reference diameter where the DCB is the same size as the predilatation lumen. In that case, inflate gently with slow pressure, the lowest possible pressure for indentation achievement, and a long inflation period to avoid severe dissection.

Step 5. After predilatation, perform repeat angiographic and IVUS evaluation. In many cases, even if severe dissection was seen on angiography, the patient might be followed-up once without additional intervention if there is no flow limitation; in many cases, the vessel dissection may have healed in the chronic phase. Select a DCB size that is the same size as the reference vessel diameter as assessed by IVUS, and complete the procedure with > 3 minutes of inflation.

Case 2: "Leave Scaffolding Behind" Under IVUS Evaluation

An example of cases treated with DES and SG under IVUS evaluation can be seen in Figures 5 and 6, respectively.

Step 1. From the initial angiogram, roughly identify the lesion length, vessel diameter, calcification severity, and distal/proximal landing position.

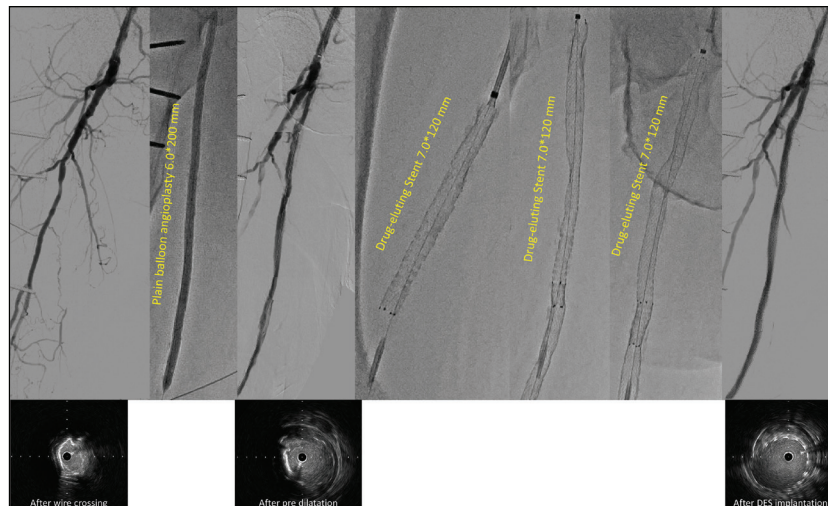


Figure 5. A representative case of DES treatment under IVUS evaluation. Despite the presence of severe calcification, IVUS shows that the stent is well-expanded due to an aggressive vessel preparation.

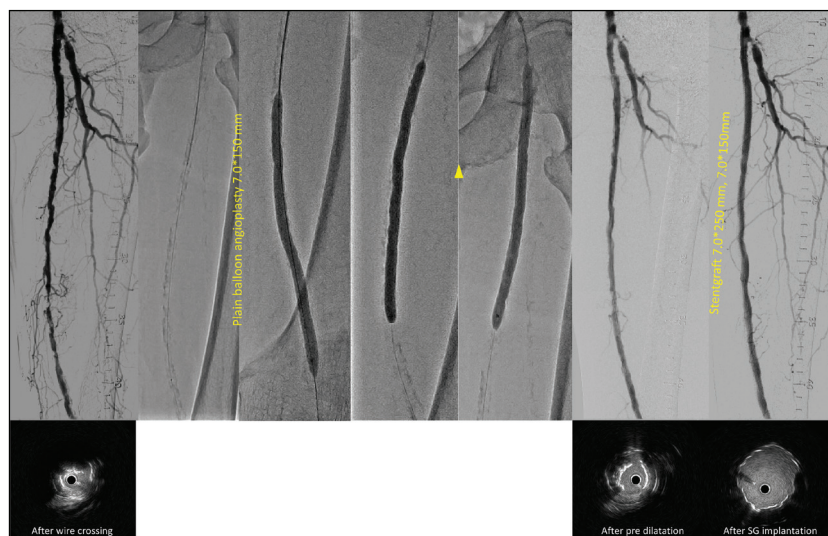


Figure 6. A representative case of SG treatment under IVUS evaluation. Despite the presence of severe calcification, IVUS shows that the stent is well-expanded due to an aggressive vessel preparation.

Step 2. Precisely identify a plaque-free, healthy distal landing position for the stent landing and evaluate the diameter of the vessel in that area.

Step 3. Subsequently, pull back the IVUS catheter and evaluate the diameter the entire vessel. Calcification severity is also evaluated at this time.

Step 4. Predilate with a balloon the same size as or 1 mm larger than the distal reference diameter. The main purpose of predilatation in the leave scaffolding strategy is to obtain a large lumen. A high degree of dissection is evidence of adequate predilatation. Predilatation here

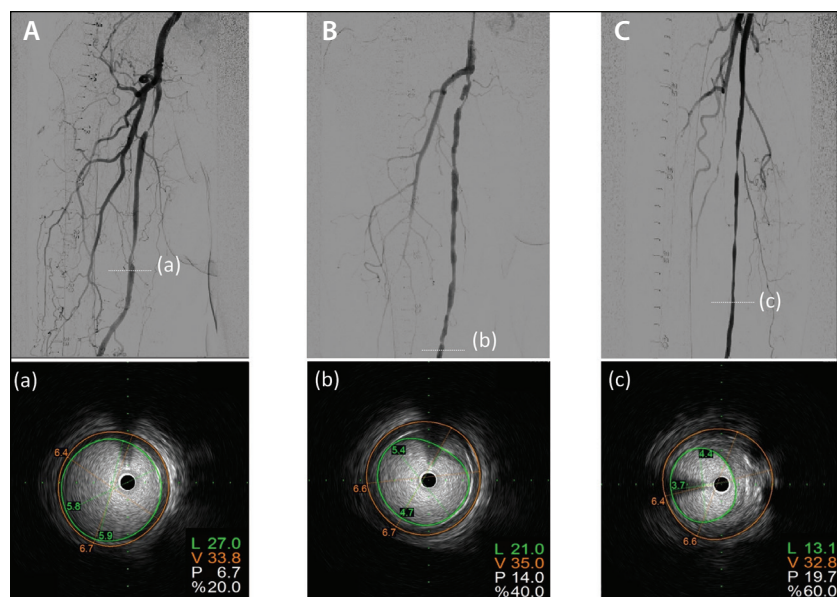


Figure 7. Representative cases with 20% (A), 40% (B), and 60% (C) plaque burden evaluated by IVUS and angiography.

differs from predilatation before DCB treatment in that it is a more aggressive attempt at high pressure. Long inflation is only indicated if there is contrast leak after stenting.

Step 5. After predilatation, reevaluate the vascular condition using angiography and IVUS, and reevaluate the distal EEM reference assessed using IVUS. If using a DES or BMS, place a stent that is sized 1 mm larger than the reference EEM to avoid excessive oversizing.

Step 6. Perform postdilatation after stent placement according to distal reference EEM or stent diameter using a noncompliant balloon. As shown in Figures 5 and 6, an almost round-shaped expansion was achieved after aggressive postdilatation using a noncompliant balloon. Always measure the minimum stent area of the stenting site using IVUS.

IN-STENT RESTENOSIS AND IVUS

Although the nitinol stent has emerged clinically as a major advance in the treatment of FP disease since the introduction of percutaneous transluminal angioplasty, the development of neointimal hyperplasia within the stent leading to the occurrence of in-stent restenosis (ISR) is the main limitation to long-term success among stent-supported endovascular approaches. In clinical settings, a substantial incidence of recurrence is unavoidable, and clinical outcomes after reintervention for ISR have been shown to vary considerably between different patterns of ISR. In particular, outcomes after reintervention for ISR-related occlusion are suboptimal.²³

Therefore, it is important to distinguish ISR-related occlusion from nonocclusive ISR lesions.

We recently investigated predictors of ISR-related occlusion after FP artery stent placement with IVUS evaluation in patients with symptomatic PAD and FP artery lesions.²⁴ After multivariate analysis, plaque burden $\geq 60\%$ after stent placement ($P < .001$), female sex, and Trans-Atlantic InterSociety Consensus II classification C/D lesions were significantly associated with the occurrence of ISR-related occlusion involving the stent edge. Consequently, if stent implantation is applied to FP lesions, the stent landing position at the proximal and distal site should be a plaque-free position to prevent future occurrence of ISR-related occlusion.

As mentioned previously, there is a relevant gap of evidence regarding vessel morphology assessed by IVUS versus angiography. Given these results, IVUS plays an important role in detecting a landing position with plaque burden $< 60\%$.

What Is Plaque Burden?

As mentioned previously, key tips and tricks for prevention of ISR-related occlusion is to precisely identify the characteristics of the stent landing position, especially the degree of plaque burden. How can we evaluate plaque burden using IVUS?

Plaque burden (Figure 7) is defined as the area between the EEM and lumen leading edges, which is calculated as the proportion of the entire EEM occupied by atherosclerotic plaque throughout the segment of interest using the following equation: plaque burden = $\Sigma(\text{EEM area} - \text{lumen area}) / \Sigma \text{EEM area} \times 100$.

Plaque burden is generally calculated after stent implantation using IVUS evaluation at a site within 5 mm of the stent's edge. The site with the greatest plaque burden between the proximal and distal sites is extracted and calculated from the reference cross-sectional area divided by the EEM cross-sectional area.

It is important to understand the clinical consequences after stent implantation for landing positions with plaque burden $> 60\%$ (Figure 8). The percentage of stent patency, restenosis, and ISR-related occlusion were analyzed when classifying groups by plaque burden with a cutoff of 60%. In the group with $> 60\%$ plaque burden

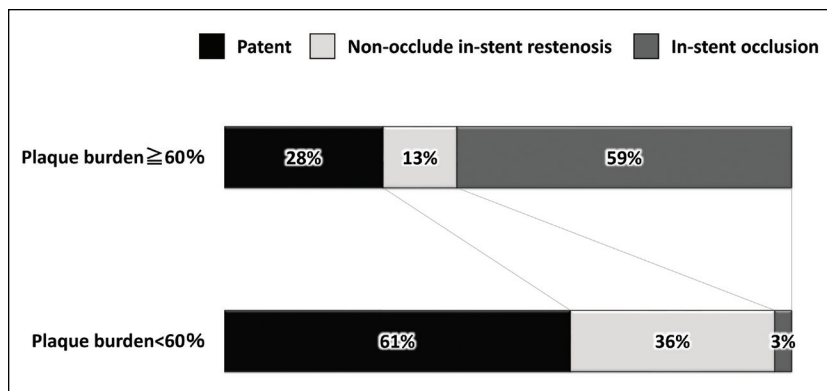


Figure 8. The percentage of stent patency, nonoccluding ISR, and ISR-related occlusion (ie, in-stent occlusion) according to plaque burden ($\geq 60\%$ or $< 60\%$).

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after stent placement, the incidence of ISR-related occlusion was the greatest, accounting for 59% of all lesions with ISR-related occlusions.²⁴

SUMMARY

IVUS undeniably provides plentiful information. We must not only use IVUS to provide the best EVT in individual cases but also to carefully collect and analyze data to build accurate knowledge about the pre- and post-procedural vessel and lesion characteristics that influence clinical outcomes. These findings are vital for risk stratification at present and for procedural development and improvement in the future. ■

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