Clinical Evidence of Intravascular Ultrasound-Guided Percutaneous Coronary Intervention

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Intravascular ultrasound (IVUS) provides anatomic information regarding the coronary artery lumen, wall, and plaques, which can help the accurate evaluation of lesion characteristics with vessel sizing. In addition, after stent implantation, underexpansion, malapposition, or edge dissections can be detected by IVUS. Thus, through further intervention based on these IVUS findings, stent optimization can be achieved, causing the improved clinical outcomes. Current guidelines recommend the use of IVUS to optimize stent implantation for select patients (Class of recommendation IIa, Level of evidence B) [1, 2]. However, recently, many evidences demonstrating the clinical usefulness of IVUS have been accumulated since the prior guidelines were released. In this chapter, clinical evidences of IVUS-guided percutaneous coronary intervention (PCI) will be discussed from observational studies, randomized studies, and meta-analysis.

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5.1 Clinical Studies Evaluating Clinical Usefulness of IVUS-Guidance PCI

Several randomized clinical trials were performed to demonstrate clinical usefulness of IVUS-guidance during PCI. Recently conducted randomized controlled trials comparing IVUS-guidance vs. angiography-guidance particularly using the drug-eluting stent (DES) are summarized in Table 5.1 [3-10]. The first two trials by Jakabacin et al. and Cheiffo et al. failed to prove the clinical benefit of IVUS-guidance because of relatively small number of patients, less than 150 patients in each group were included in their studies [3, 4]. Kim et al. reported that IVUS usage for diffuse long lesions was associated with improved clinical outcomes particularly when used by operators' decision. In the per-protocol analysis, IVUSguidance group significantly had lower 1-year major adverse cardiovascular event (MACE) (4.0% vs. 8.1%, p = 0.048), although the strategy of routine IVUS for DES implantation did not improve the MACE rates in the intentionto-treat analysis [5]. Recent randomized trials which showed statistically significant clinical benefit were performed mainly for complex lesions, such as left main lesions [7], chronic

Study	Year	<i>N</i> (IVUS vs. angiography)	Enrolled patients	Follow-up, <i>m</i>	Primary endpoint	Major findings (IVUS vs. angiography)
Jakabacin et al. [3]	2010	105 vs. 105	Complex cases and high clinical risk profile	18	Composite of death, MI, TLR	No significant differences (11% vs. 12%)
Chieffo et al. [4]	2013	142 vs. 142	Complex lesions	24	Post-procedural in-lesion MLD	IVUS group had greater MLD (2.70 mm vs. 2.51 mm, p = 0.002)
Kim et al. [5]	2013	269 vs. 274	Long lesions (implanted stent ≥ 28 mm in length)	12	Composite of cardiovascular death, MI, stent thrombosis, or TVR	No significant differences by intention-to-treat analysis; but IVUS group had lower primary endpoint by per-protocol analysis (4.0% vs. 8.1%, p = 0.048)
MOZART [6]	2014	41 vs. 42	High risk of contrast- induced acute kidney injury or volume overload	-	Total volume contrast agent used during PCI	IVUS group had lower volume contrast agent (20 ml vs. 65 ml, <i>p</i> < 0.001)
Tan et al. [7]	2015	62 vs. 61	Unprotected LM in the elderly (aged 70 or older)	24	Composite of death, non-fatal MI, or TLR	IVUS group had lower primary endpoint (13.1% vs. 29.3%, $p = 0.031$)
CTO- IVUS [8]	2015	201 vs. 201	Chronic total occlusion	12	Cardiac death	No significant differences in primary endpoint; but IVUS group had lower secondary endpoint (the composite of cardiac death, MI, or TVR) (2.6% vs. 7.1%, $p = 0.035$)
Tian et al. [9]	2015	115 vs. 115	Chronic total occlusion	12	Late lumen loss	IVUS group had a lesser late lumen loss (0.28 mm vs. 0.46 mm, $p = 0.025$)
IVUS- XPL [<mark>10</mark>]	2015	700 vs. 700	Long lesions (implanted stent ≥28 mm in length)	12	Composite of cardiac death, MI, or TLR	IVUS group had lower primary endpoint (2.9% vs. 5.8% , $p = 0.007$)

 Table 5.1
 Recent randomized studies comparing clinical usefulness between IVUS-guided and angiographyguided PCI

IVUS intravascular ultrasound, *LM* left main, *MI* myocardial infarction, *MLD* minimal lumen diameter, *PCI* percutaneous coronary intervention, *TLR* target-lesion revascularization, *TVR* target-vessel revascularization

total occlusions (CTO) [8, 9], and diffuse long lesions [10]. The CTO-IVUS (Chronic Total Occlusion InterVention with drUg-eluting Stents) study, the first randomized trial for CTO lesions, demonstrated that IVUS-guided PCI may improve 12-month MACE rates after DES implantation when compared with conventional angiography-guided CTO-PCI [8]. In the IVUS-XPL (Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions) trial, IVUS-guided DES implantation compared with angiographyguided DES implantation resulted in a significantly lower rate of the composite of MACE (a composite of cardiac death, myocardial infarction [MI], or target-lesion revascularization [TLR]) at 1 year (2.9% vs. 5.8%, hazard ratio [HR] = 0.48, p = 0.007) [10]. These differences were primarily due to lower risk of TLR (2.5% vs. 5.0%, HR = 0.51, p = 0.02).

According to the ADAPT-DES (The assessment of dual antiplatelet therapy with drugeluting stents) study, the most recent largest observational study with all-comers (n = 8583)[11], IVUS was utilized in 3349 patients (39%), and larger-diameter devices, longer stents, and/or higher inflation pressure were used in the IVUSguided cases. At 1 year, propensity-adjusted multivariable analysis revealed IVUS-guidance vs. angiography-guidance was associated with a reduced definite/probable stent thrombosis (0.6% vs. 1.0%, p = 0.003), MI (2.5% vs. 3.7%, p = 0.004), and composite adjudicated major cardiac events (cardiac death, MI, or stent thrombosis) (3.1% vs. 4.7%, p = 0.002). The benefits of IVUS were especially evident in patients with acute coronary syndromes and complex lesions [11]. Further recent observational studies evaluating clinical usefulness of IVUS-guided PCI are summarized in Table 5.2 [11–17].

Lastly, meta-analyses comparing the IVUSguidance and angiography-guidance are presented in Table 5.3 [18-22]. Shin et al. reported the results of meta-analysis with individual patient-level data from 2345 randomized patients. IVUS-guided new-generation DES implantation vs. angiography-guided DES implantation was associated with a favorable outcome, particularly the occurrence of hard clinical endpoint (the composite of cardiac death, MI, or stent thrombosis) for complex lesions [22]. Of note, the primary endpoint of this meta-analysis did not include TLR. Therefore, different from the IVUS-XPL trial showing the benefit of IVUS due primarily to the less frequent TLR events [10], MACEs, even excluding the TLR events in this meta-analysis, were less frequent with IVUSguidance than angiography-guidance [22].

Table 5.2 Recent observational studies comparing clinical outcomes between IVUS-guided and angiography-guided PCI

			Enrolled	Follow-up,	Major findings
Study	Year	angiography) p	patients	т	(IVUS vs. angiography)
Witzenbichler et al. [11]	2014	3349 vs. 5234	All comers	12	Definite/probable ST: 0.6% vs. 1.0%, p = 0.003 MI: 2.5% vs. 3.7%, $p = 0.004$ Composite of cardiac death, ST, MI; 3.1% vs. 4.7%, $p = 0.002$
Roy et al. [12]	2008	884 vs. 884 by A matching	All comers	12	Definite ST: 0.7% vs. 2.0%, <i>p</i> = 0.014
Park et al. [13]	2013		Nearly all comers	12	Composite of cardiac death, MI, TLR: 4.3% vs. 2.4, $p = 0.047$
Youn et al. [14]	2011		Primary PCI cases	36	Composite of death, MI, TLR, TVR: 12.8% vs. 18.1%, $p = NS$
Kim et al. [15]	2011		Non-left main oifurcation	36	Death or MI: 3.8% vs. 7.8% , $p = 0.03$
Hong et al. [16]	2014		Chronic total occlusion	24	Definite/probable ST: 0% vs. 3.0%, <i>p</i> = 0.014 MI: 1.0% vs. 4.0%, p = 0.058
de la Torre Hernandez et al. [17]	2014		Left main esions	36	Composite of cardiac death, MI, TLR: 11.3% vs. 16.4%, $p = 0.04$ Definite/probable ST: 0.6% vs. 2.2%, p = 0.04

IVUS intravascular ultrasound, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *ST* stent thrombosis, *TLR* target-lesion revascularization, *TVR* target-vessel revascularization, *NS* non-significant

Study	Year	N (analyzed studies)	<i>N</i> (IVUS vs. angiography)	Data analysis	Major findings (IVUS vs. angiography)
Jang et al. [18]	2014	3 RCTs and 12 observational studies with DES implantation	11,793 vs. 13,056	Study-level meta-analysis	IVUS had lower MACE (OR = 0.79 , $p = 0.001$), all-cause mortality (OR = 0.64 , $p < 0.001$), MI (OR = 0.57 , $p < 0.001$), TVR (OR = 0.81 , $p = 0.01$), and ST (OR = 0.59 , $p = 0.002$)
Ahn et al. [19]	2014	3 RCTs and 14 observational studies with DES implantation	12,499 vs. 14,004	Study-level meta-analysis	IVUS had lower TLR (OR = 0.81 , $p = 0.046$), death (OR = 0.61 , $p < 0.001$), MI (OR = 0.57 , p < 0.001), and ST (OR = 0.59 , $p < 0.001$)
Elgendy et al. [20]	2016	7 RCTs with DES implantation	1593 vs. 1599	Study-level meta-analysis	IVUS group had lower MACE at a mean of 15 months (6.5% vs. 10.3%, $p < 0.0001$), mainly because of reduction in the risk of TLR (4.1% vs. 6.6%, $p = 0.003$)
Steinvil et al. [21]	2016	7 RCTs and 18 observational studies with DES implantation	14,659 vs. 16,624	Study-level meta-analysis	IVUS group had lower MACE (OR = 0.76, $p < 0.001$), death (OR = 0.62, $p < 0.001$), MI (OR = 0.67, $p < 0.001$), ST (OR = 0.58, $p < 0.001$), TLR (OR = 0.77, $P = 0.005$), and TVR (OR = 0.85 $p < 0.001$)
Shin et al. [22]	2016	3 RCTs with new-generation DES implantation	1170 vs. 1175	Individual patient-level meta-analysis	IVUS group had a lower occurrence of hard clinical outcome (composite of cardiac death, MI, or ST) at 1 year (0.4% vs. 1.2% , $p = 0.04$)

 Table 5.3
 Recent meta-analyses comparing clinical outcomes between IVUS-guided and angiography-guided PCI

DES drug-eluting stent, *IVUS* intravascular ultrasound, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *OR* odds ratio, *RCT* randomized clinical trial, *ST* stent thrombosis, *MI* myocardial infarction, *TLR* target-lesion revascularization, TVR = target-vessel revascularization

5.2 Left Main Lesion

Procedural complication or failure of left main lesion of PCI is critical. Thus, IVUS-guidance PCI for left main lesion is currently recommended as a class IIa or class IIb recommendation [1, 2]. In addition to the stent optimization, particularly for left main lesions, functionally significant lesion can be relatively accurately predicted by IVUS examination for intermediate lesions because of the limited variability of left main coronary artery length, diameter, and the amount of supplied myocardium. Minimal lumen area (MLA) less than 4.5 mm² predicted the fractional flow reserve (FFR) less than 0.80 with sensitivity of 77% and specificity of 82% [23]. Other studies also reported the optimal cutoff value of MLA by IVUS for predicting functionally significant left main lesions (FFR less than 0.75) were 5.9 mm² and 4.8 mm², respectively [24, 25]. IVUS is also essential for the optimization to reduce the restenosis. A previous study showed that the cut-off values of poststenting MLA that best predicted in-stent restenosis were 5.0 mm² in ostial left circumflex, 6.3 mm² in ostial left anterior descending, 7.2 mm² in polygon of confluence, and 8.2 mm² in left main [26].

Recently, a randomized trial for unprotected left main lesions revealed that IVUS-guided group had a lower composite of death, non-fatal MI, or TLR (13.1% vs. 29.3%, p = 0.031), although small number of patients were studied in this study [7]. Also, a recent pooled analysis from 4 Spanish registries demonstrated that IVUS-guided DES implantation for unprotected left main showed a lower 3-year composite rate of cardiac death, MI, and TLR compared with the angiography-guided DES implantation (11.3% vs 16.4%, p = 0.04), and a more prominent in the subgroup with distal left main lesions (10.0% vs 19.3%, p = 0.03) [17].

5.3 Bifurcation Lesion

There were no randomized studies performed particularly for the bifurcation lesions. According to the observational studies, Kim et al. demonstrated that the 3-year cumulative incidence of death or MI was significantly lower in the IVUS-guided PCI group than the angiography-guided PCI group (3.8% vs 7.8%, p = 0.03) [15]. Another observational study with bifurcation lesions, the rate of TLR was significantly lower in the IVUSguided PCI group (6% vs 21%, p = 0.001) [27]. In the first study, two-stent technique and final kissing balloon were more frequently used in the IVUS-guidance group [15], whereas in the second study, the number of implanted stents was significantly lower in the IVUS-guidance group [27]. In this regard, although further studies are needed to determine the optimal stent strategies including the stent number particularly for bifurcation lesions, the role of IVUS for the decision of stent strategies may be important to improve clinical outcomes for the complex bifurcation lesions. A previous study evaluated the IVUS parameters predicting the IVUS $\geq 4 \text{ mm}^2$ at 9-month followup IVUS for both main vessel and side branch after bifurcation T-stenting with first-generation DES [28]. Inadequate post-procedural minimal stent area (MSA) with increased neointimal hyperplasia may cause the side branch ostium to be the most frequent restenotic site after bifurcation PCI and the optimal cut-off value of postprocedural MSA was 4.83 mm² [28].

5.4 Chronic Total Occlusion

The roles of IVUS for CTO intervention could be classified into 3 different uses: (1) wire-crossing for the stumpless CTO lesions, (2) pre-stenting use, and (3) post-stent use. For the stumpless CTO lesions, IVUS-guidance has been reported to lead a higher success rate and to be useful in revealing the entry point of occlusion and in repositioning a guidewire in the event of inadvertent sub-intimal passage [29]. Pre-stenting IVUS could provide the accurate information regarding vessel size and lesion length and cause resultant appropriate stent size and length for stent optimization. CTO vessel often increases in size following the successful CTO PCI. An IVUS follow-up study at 6 month after CTO PCI revealed that distal lumen diameter was increased in two thirds of patients by 0.4 mm (p < 0.001) [30]. Post-stent IVUS may detect PCI complications or suboptimal stent expansion and could lead to stent optimization and finally can decide the need for additional stenting or ballooning. However, there had been a lack of evidence regarding the beneficial role of IVUS-guided CTO intervention using current-generation DES for the improved clinical outcomes after stent implantation. Two randomized trials were performed particularly for CTO lesions [8, 9]. In the CTO-IVUS trial, 402 patients with CTOs were randomized to the IVUS-guided group (n = 201) or the angiography-guided group (n = 201) after successful guidewire crossing [8]. Although IVUS-guided CTO intervention did not significantly reduce cardiac mortality, IVUSguided CTO intervention improved 12-month MACE rate after new-generation DES implantation when compared with conventional angiography-guided CTO intervention. In this study, IVUS-guidance group had a higher proportion of high-pressure post-stent dilation (51% vs. 41%, p = 0.045) with a higher maximum poststent balloon pressure (14.6 vs. 13.8 atm, p = 0.040). Consequently, the post-procedural minimal lumen diameter was significantly larger in the IVUS-guidance vs. angiography-guidance (2.64 vs. 2.56 mm, p = 0.025).

In the second randomized trial, Tian et al. reported stent late lumen loss at 1 year between IVUS- vs. angiography-guidance [9]. Late lumen loss was significantly lower in the IVUS-guided group compared with the angiography-guided group (0.28 vs 0.46 mm, p = 0.025), although these angiographic findings were not translated into the improvement of clinical outcomes.

5.5 Diffuse Long Lesion

A long lesion inevitably increases the length of implanted stent, and long stent increases the incidence of stent underexpansion. In the IVUS-XPL enrolling 1400 patients requiring ≥28 mm everolimus-eluting stents, adjunct post-stent balloon dilation was more frequently performed in the IVUS-guided stent group (76%) than in the angiography-guided stent group (76% vs 57%, p < 0.001 [10]. The mean final balloon size was larger in the IVUS-guided group than in the angiography-guided group. On post-procedural quantitative angiography analysis, minimum lumen diameter was greater and diameter stenosis was smaller in the IVUS-guided stent group than in the angiography-guided stent group [10]. In addition, in the post hoc analysis in that study among the patients within the IVUS-guided stent group, the patients who did not meet the IVUS criteria (n = 315, 46%) had a significantly higher incidence of the primary endpoint compared with those meeting the IVUS criteria for stent optimization (n = 363, 54%) (4.6% vs 1.5%, p = 0.02), when IVUS criteria for stent optimization after PCI was defined as an MLA greater than the lumen cross-sectional area at the distal reference segments [10].

5.6 In-Stent Restenosis

The use of IVUS to guide PCI for the treatment of restenosis is a class IIa recommendation in the current PCI guidelines [1, 2]. IVUS can differentiate whether restenosis is related to intimal hyperplasia or mechanical complications, such as stent fracture or underexpansion. According to the recent IVUS study comparing the mechanisms and patterns of in-stent restenosis among bare metal stents and DES, restenotic first- and second-generation DES were characterized by less neointimal hyperplasia, smaller stent areas, longer stent lengths, and more stent fractures [31].

5.7 Patients with Chronic Kidney Disease

Patients with chronic kidney disease (CKD) comprise a challenging subset of patients because of the increased incidence of contrast-induced acute

injury following angiography kidney and PCI. Considerable efforts have been made to reduce contrast volume particularly in patients with CKD. Although most randomized clinical trials measured clinical or angiographic outcomes, the MOZART (Minimizing cOntrast utiliZation With IVUS Guidance in coRonary angioplasty) trials measured the total volume contrast agent used during PCI as the primary endpoint [6]. In this trial, a total of 83 patients with a high risk of contrast-induced acute kidney injury or volume overload were randomized to IVUS-guided PCI or angiography-guided PCI, and IVUS group had a lower total volume of contrast (20 ml vs. 65 ml, p < 0.001). Also, recent another study with a total of 31 patients with advanced CKD (creatinine = 4.2 mg/dL) revealed that PCI without contrast using IVUS and physiologic guidance may be performed safely with high procedural success and without complications [32].

5.8 IVUS Predictors for the Better Clinical Outcomes: Stent Optimization

The IVUS predictors of stent failure after DES implantation are underexpansion, dissections, and significant plaque burden (Table 5.4) [33-35]. When a total of 804 patients who underwent both post-intervention IVUS examination after long everolimus-eluting stent (≥28 mm in length) implantation were analyzed from two randomized trials (RESET trial and IVUS-XPL trial), the predictors of MACE were the postintervention MLA at the target lesion and the ratio of MLA/distal reference segment lumen area [33]. The MLA and MLA-to-distal reference segment lumen area ratio that best predicted patients with MACE from those without it were 5.0 mm² and 1.0, respectively. Patients with an MLA $< 5.0 \text{ mm}^2$ or a distal reference segment lumen area had a higher risk of MACE than those without MACE (HR = 6.2, p = 0.003). Similarly, Song et al. reported that the optimal MSA to predict angiographic restenosis at 9 months were 5.3 mm² for zotarolimus-eluting stents and 5.4 mm² for everolimus-eluting stents [34]. Therefore, the confirmation of sufficient MLA by IVUS is important after DES implantation. Figure 5.1 represents the stent underexpansion detected by IVUS examination despite of angiographically acceptable diameter stenosis, suggesting the need of post-stent adjuvant ballooning. Figure 5.2 represents the achievement of sufficient MLA after post-stent adjuvant ballooning.

	N	Follow-up endpoint	Stent	IVUS parameter after stenting	Cut-off value	Accuracy
Lee et al. [33]	804	MACE (cardiac death, MI, and TLR)	EES	MLA MLA/distal reference lumen area	5.0 mm ² 1.0	Patients with an MLA < 5.0 mm^2 or a distal reference segment lumen area had a higher risk of MACE (hazard ratio = 6.231 , $p = 0.003$) than those without MACE
Song et al. [34]	229 220	Angiographic in-stent restenosis	EES ZES	MSA	5.4 mm ² 5.3 mm ²	Sensitivity 60%, specificity 60% Sensitivity 57%, specificity 62%
Kang et al. [35]	433 422 813	Angiographic edge restenosis	E-ZES R-ZES EES	Edge plaque burden	56.3% 57.3% 54.2%	Sensitivity 67%, specificity 86% Sensitivity 80%, specificity 87% Sensitivity 86%, specificity 80%

Table 5.4 IVUS parameter after newer generation DES implantation predicting angiographic restenosis or MACE

EES everolimus-eluting stent, *E-ZES* Endeavor zotarolimus-eluting stents, *IVUS* intravascular ultrasound, *MACE* major adverse cardiovascular event, *MLA* minimal lumen area, *MSA* minimal stent area, *R-ZES* Resolute zotarolimus-eluting stents

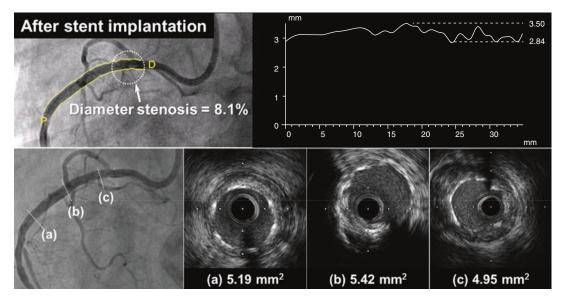


Fig. 5.1 Representative case showing the stent underexpansion by IVUS despite of angiographically acceptable diameter stenosis. After implantation of everolimuseluting stent (Xience prime 2.75×38 mm, Abbott Vascular) for diffuse stenosis of right coronary artery, the residual stenosis by angiography at proximal portion of

the stent was 8.1%, which was angiographically acceptable. However, on IVUS evaluation, the MLA was measured 4.95 mm² (c), which was smaller than the distal reference lumen area of 5.19 mm² (a) and less than 5 mm², suggesting the need of post-stent adjuvant ballooning

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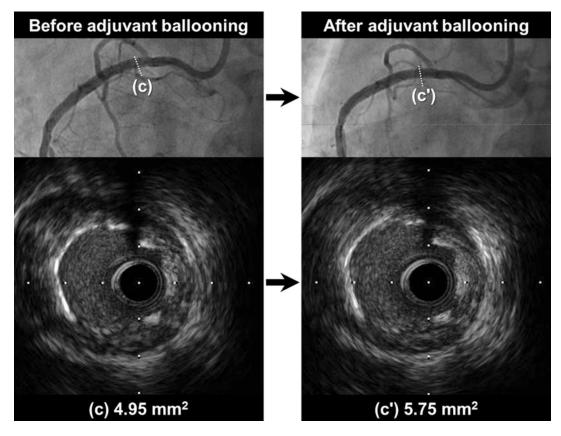


Fig. 5.2 Representative case showing the achievement of sufficient minimal lumen area measured by IVUS after post-stent adjuvant ballooning. After post-stent adjuvant ballooning with 3.0 mm-sized non-compliant balloon

catheter based on the findings of IVUS, the minimal lumen was increased from 4.95 mm² to 5.75 mm². Same patients presented in Fig. 5.1

Kang et al. evaluated IVUS predictors for angiographic edge restenosis after newer generation DES [35]. The predictive cut-off of the reference plaque burden was 56.3% for Endeavor zotarolimus-eluting stents, 57.3% for Resolute zotarolimus-eluting stents, and 54.2% for everolimus-eluting stents. Figure 5.3 presents the representative case showing the need of additional stenting at proximal segment of stent because of edge dissection and residual plaque more than 60%, even though angiographic findings were acceptable.

Although IVUS studies have reported that the late stent malapposition is a predictor of late or very late stent thrombosis, there is no data linking isolated acute stent malapposition without stent underexpansion to early stent thrombosis or restenosis [36].

From the bare-metal stent era, the need for a standard to examine the stent optimization led to the formation of IVUS defined criteria. IVUS criteria for stent optimization used in the recent randomized clinical trials were summarized in Table 5.5 [3, 8-10]. Despite the need for a consensus, several different criteria have been employed in different clinical studies. However, according to the previous studies and the criteria used in recent trials, the achievement of sufficient lumen area by IVUS may be imperative.

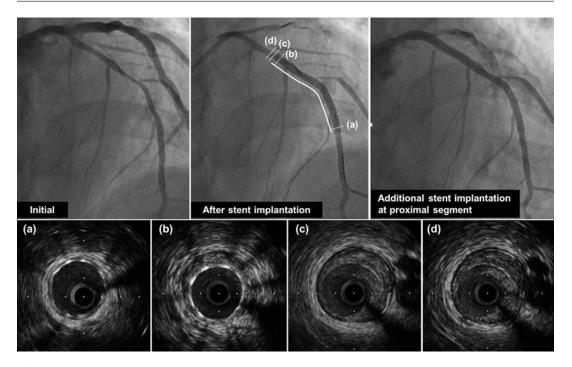


Fig. 5.3 Representative case showing the need of additional stenting at proximal segment of stent because of edge dissection and residual plaque. Although angiographic findings were acceptable, another stent was addi-

tionally implanted at the proximal segment based on the IVUS finding, (c) the dissection at the proximal edge of the stent with (d) residual plaque more than 60%

Table 5.5 IVUS criteria for stent optimization used in recent randomized clinical trials

Study	IVUS criteria for stent optimization
Jakabacin et al. [3]	 Good apposition Optimal stent expansion [with MSA of 5 mm²] or CSA > 90% of distal reference lumen CSA for small vessel No edge dissection (5-mm margins proximal and distal to the stent)
CTO- IVUS [8]	 MSA ≥ distal reference lumen area Stent area at CTO segment ≥5 mm² as far as vessel area permits Complete stent apposition
Tian et al. [9]	 Good apposition Stent MSA >80% of reference vessel area Symmetric index >70% No > Type B dissection
IVUS- XPL [10]	(1) A minimal lumen CSA greater than the lumen CSA at distal reference segments

CSA cross-sectional area, MSA minimal stent area

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