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Current Clinical Applications of Intravascular Ultrasound in Coronary Artery Disease

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Abstract
Purpose of Review During the 20 years since the introduction of intravascular ultrasound (IVUS) to catheterization laboratory, there has been growing evidence supporting the role of IVUS. In this article, we review clinical application of routine use of IVUS with recent evidences, a dominant strategy even in the era of drug-eluting stents.
Recent Findings IVUS provides pre-procedural information to evaluate stenosis severity and plaque characteristics. In addition, IVUS helps optimal stent deployment, minimizing underexpansion and geographic miss, which are major mechanisms of stent failure. Large-scale clinical trials and meta-analyses have shown that the clinical benefits of IVUS guidance are maximized in complex lesions (left main coronary artery, long lesions and chronic total occlusion). Some recent studies have also supported the cost effectiveness of IVUS-guided PCI especially when there is a high risk of stent failure.
Summary IVUS provides valuable information about lesion severity, lumen and vessel size, lesion length, and plaque characteristics. By determining appropriate stent sizes and optimizing stenting procedures, IVUS-guided PCI improves clinical outcomes especially in patients with high-risk coronary lesions.

Keywords Intravascular ultrasound · Percutaneous coronary intervention · Stent thrombosis · Restenosis

Abbreviations

AMI	Acute myocardial infarction
BMS	Bare-metal stent
CTO	Chronic total occlusion
DES	Drug-eluting stent
FFR	Fractional flow reserve
ISR	In-stent restenosis
IVUS	Intravascular ultrasound
LAD	Left anterior descending
LMCA	Left main coronary artery
MLA	Minimum lumen area
MACE	Major adverse cardiac events
MI	Myocardial infarction
MSA	Minimum stent area
PCI	Percutaneous coronary intervention
SES	Sirolimus-eluting stent
ST	Stent thrombosis
STEMI	ST-segment elevation MI

Introduction

Since intravascular ultrasound (IVUS) was introduced in the early 1990s, it has brought profound scientific insights to the understanding of the pathophysiology of coronary artery disease and to clinical decision-making. With a spatial resolution of >150–200 μm, IVUS provides valuable information about stenosis severity, lumen and vessel morphology, lesion length, and plaque characteristics, complementing angiographic images. Current guidelines recommend the use of IVUS for assessing indeterminate left main coronary artery disease and

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cardiac allograft vasculopathy after heart transplantation (Class IIa). In addition, IVUS is useful for determining the mechanism of stent restenosis (Class IIa) [1, 2]. There are abundant prospective and retrospective data validating the clinical impact of IVUS-guided percutaneous coronary intervention (PCI) and imaging criteria for PCI optimization. Previously, clinical application of IVUS was shown in "Standards for the Acquisition, Measurement, and Reporting of Intravascular Ultrasound Studies: A Report of the ACC Task Force on Clinical Expert Consensus Documents" [3]. In this review, we discuss the role of IVUS in daily practice and its clinical implications, supported by more recent evidences.

Pre-procedural Lesion Evaluation

Severity of Stenosis

Lesion-specific fractional flow reserve (FFR) is considered to be the gold standard for assessing the physiologic significance of coronary artery disease [1, 2, 4–7]. The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) trial, which included 1005 patients with multivessel disease, demonstrated that FFR-guided PCI resulted in a significantly lower rate of the composite endpoint of death, myocardial infarction (MI) and repeat revascularization compared with angiography-guided PCI [7]. With the current paradigm shift to functional angioplasty, the use of IVUS-derived minimal lumen area (IVUS-MLA) as a surrogate marker for ischemia-producing lesions has been under debate.

Non-left Main Coronary Artery

Table 1 summarizes much of the published data validating IVUS-MLA criteria for predicting an FFR of <0.75–0.80 in non-left main coronary artery (non-LMCA) lesions. Although IVUS-MLA thresholds varied from 2.0 to 4.0 mm^2, their diagnostic accuracies were approximately 70% [8–20]. The overall mean MLA cutoff value from a recent meta-analysis was approximately 2.6 mm^2 [21, 22]. Recent studies have attempted to identify subgroup-specific MLA cutoffs according to vessel size and lesion location because the FFR value is influenced by the amount of myocardium subtended to the post-stenotic segment [12–15, 16••, 19, 20]. For lesions of the mid left anterior descending (LAD) artery or those with a reference vessel diameter of <3.0 mm, the IVUS-MLA cutoff ranges from 2.0 to 2.6 mm^2. For lesions of the proximal LAD artery or those with a reference vessel diameter of >3.0 mm, the IVUS-MLA cutoff ranges from 2.8 to 3.2 mm^2 [10, 12, 15, 16••, 19, 20]. There is also a trend for the MLA cutoff for LAD artery lesions to have better accuracy for predicting FFR compared with those of other coronary vessels [12, 15, 16••]. However, the correlation between IVUS-MLA and FFR is only modest. In a recent meta-analysis including 11 clinical trials, the sensitivity and specificity of the IVUS-MLA cutoff of 2.6 mm^2 for predicting an FFR of <0.80 were 79 and 65%, respectively [21]. Functional significance is influenced by many compounding factors besides MLA including plaque characteristics, lesion location and length, plaque burden, reference vessel size, and the amount of viable myocardium subtended by the lesion; so, IVUS-MLA criteria do not accurately predict ischemia-inducing lesions [23, 24]. It is therefore not recommended for determining stenosis severity for revascularization [1, 2, 25].

Nam et al. compared FFR-guided PCI (FFR < 0.8) with IVUS-guided PCI (MLA < 4.0 mm^2) and showed similarly favorable clinical outcomes at 1-year follow-up [26]. In addition, de la Torre Herandez et al. reported no significant differences in 2-year clinical event rates between IVUS-guided PCI (MLA < 4 mm^2 in vessels of >3 mm and MLA < 3.5 mm^2 in vessels of 2.5–3 mm) and FFR-guided PCI (FFR < 0.75) [27]. Although IVUS-MLA has poor diagnostic accuracy and so cannot replace FFR measurement for assessing the functional significance of non-LMCA with its high negative predictive value, an IVUS-MLA larger than the cutoff may be useful for identifying lesions that can be safely deferred [13, 16••].

Left Main Coronary Artery

Identification of significant stenosis in LMCA is critically important because mortality benefit from revascularization is well established [28, 29]. However, coronary angiography alone has limitations when determining the significance of LMCA lesions and has considerable inter-observer variability [30]. Given the limitations of angiography, noninvasive functional tests such as myocardial perfusion imaging have complementary roles for identifying hemodynamic significance, while it is often non-contributive with balanced ischemia. Several prospective studies and meta-analyses have shown favorable clinical outcomes of FFR-guided deferral in intermediate LMCA [31–34]. A study evaluating 354 patients with LMCA disease showed that it is safe to defer revascularization with an IVUS-MLA of ≥6 mm^2 [35••].

Some studies have correlated IVUS-derived MLA with FFR in isolated LMCA disease. Jasti et al. showed a strong correlation between FFR and IVUS-MLA in angiographic ambiguous LMCA stenosis [36]. The IVUS-MLA cutoff value used to predict an FFR of <0.75 was 5.9 mm^2 (sensitivity, 93%; specificity, 95%). Kang et al. reported an IVUS-MLA of 4.8 mm^2 as the best predictor of an FFR of <0.8 (sensitivity, 89%; specificity, 83%) in isolated intermediate LM lesions [37]. Recently, Park et al. investigated 112 patients with isolated ostial and shaft LCMA stenosis and showed that an IVUS-MLA of ≤4.5 mm^2 was the optimal cutoff for an FFR of ≤0.8 (sensitivity, 77%; specificity, 82%) [38]. Although the IVUS-MLA thresholds varied among different ethnic groups,

Table 1 IVUS-derived MLA cut-off to predict FFR<0.75-0.80

Reference	Number of patient/lesion	FFR	MLA cut off (mm^2)			Sensitivity /specificity(%)	Other IVUS predictors of FFR
Takagi et al. [8]	42/51	<0.75	3.0			83/92	area stenosis
Briguori et al. [9]	43/53	<0.75	4.0			92/56	minimal lumen diameter, area stenosis, lesion length
Lee et al. [10]	94/94	<0.75	2.0			82/81	lesion length, plaque burden
Koo et al. [12]	251/267	<0.80	pLAD : 3.0 mLAD: 2.75			75/88 73/78	proximal segment, LAD
Ben-Dor et al. [11]	84/92	<0.75 <0.80	2.8 3.2			80/80 69/68	minimal lumen diameter, area stenosis, lesion length
Kang et al. [14]	692/784	<0.80	2.4	RLD <2.75 RLD 2.75-3.5	1.9 2.3	84/63	plaque burden, area stenosis
				RLD >3.5	3.2		
Ben-Dor et al. [13]	185/205	<0.80	3.09	RVD 2.5-3 RVD 3-3.5	2.4 2.7	69/79	minimal lumen diameter, area stenosis, lesion length
				RVD >3.5	3.6		
Chen et al. [15]	323/323	<0.80	2.97	RVD <3.0 RVD >3.0	2.49 3.02	83/63	plaque burden, lesion length, LAD
Waksman et al. [16]	350/367	<0.80	3.07	RVD <3.0 RVD 3.0-3.5	2.4 2.7	64/65	LAD
				RVD >3.5	3.6		
Han et al. [18]	822/881	<0.80	2.75	Asians Westerners	2.75 3.0	61/63	
Naganuma et al. [19]	109/132	<0.80	2.70	RVD <3.0 RVD >3.0	2.59 2.84	79/76	plaque burden
Yang et al. [20]	206/206	<0.80	pLAD mLAD	3.2 2.5		85/67 65/88	lesion length, percent atheroma volume
Doh et al. [17]	151/181	<0.80	2.82			84/71	

DS(%): diameter stenosis, FFR: fractional flow reserve, MLA(mm^2): minimal lumen area, RVD(mm): reference vessel diameter, LAD: left anterior descending artery.

the overall diagnostic accuracies for predicting functional significance seemed better in LMCA versus non-LMCA, which might be explained by the simplicity of the morphological characteristics of LMCA lesions [37]. However, the presence of concomitant stenosis at the proximal LAD artery or the left circumflex artery limits the practical use of IVUS-MLA in making treatment decisions [24, 39, 40].

Plaque Characteristics and Lesion Morphology

The role of grayscale IVUS in plaque characterization is limited by its poor spatial resolution using 40–45 MHz IVUS transducers. Ultrasound reflection depends on acoustic impedance of the tissue, so the grayscale IVUS approach is to compare the "brightness" of the tissue to the surrounding adventitia (Fig. 1).

Attenuated Plaque

Attenuated plaque is an IVUS finding of hypoechoic or mixed atheromas with ultrasound attenuation but little evidence of calcium [41]. Virtual histology IVUS studies have shown that attenuated plaque corresponds to large necrotic cores and thin-cap fibroatheromas, and histopathologic studies have suggested that echo attenuation is related to microcalcification, hyalinized fibrous tissue, cholesterol crystals, and lipid pools [41–44]. Histopathologically, 91.4% of echo-attenuated plaques in one study corresponded to either fibroatheroma with a necrotic core or pathological intimal thickening with a lipid pool. Fibroatheromas were found in 97% of plaques with superficial IVUS attenuation [44].

Attenuated plaque on grayscale IVUS indicates a high risk for no-reflow or post-procedural creatine kinase (CK)-MB elevation. The HORIZONS-AMI trial showed that attenuated plaque was present in over 70% of patients with acute myocardial infarction (AMI) and the amount of attenuated plaque correlated with the likelihood of no-reflow after revascularization [45]. In addition, some studies have shown that attenuated plaque is associated with stent thrombosis (ST)-segment elevation MI (STEMI), peri-procedural myocardial necrosis, and no-reflow in patients with coronary artery disease

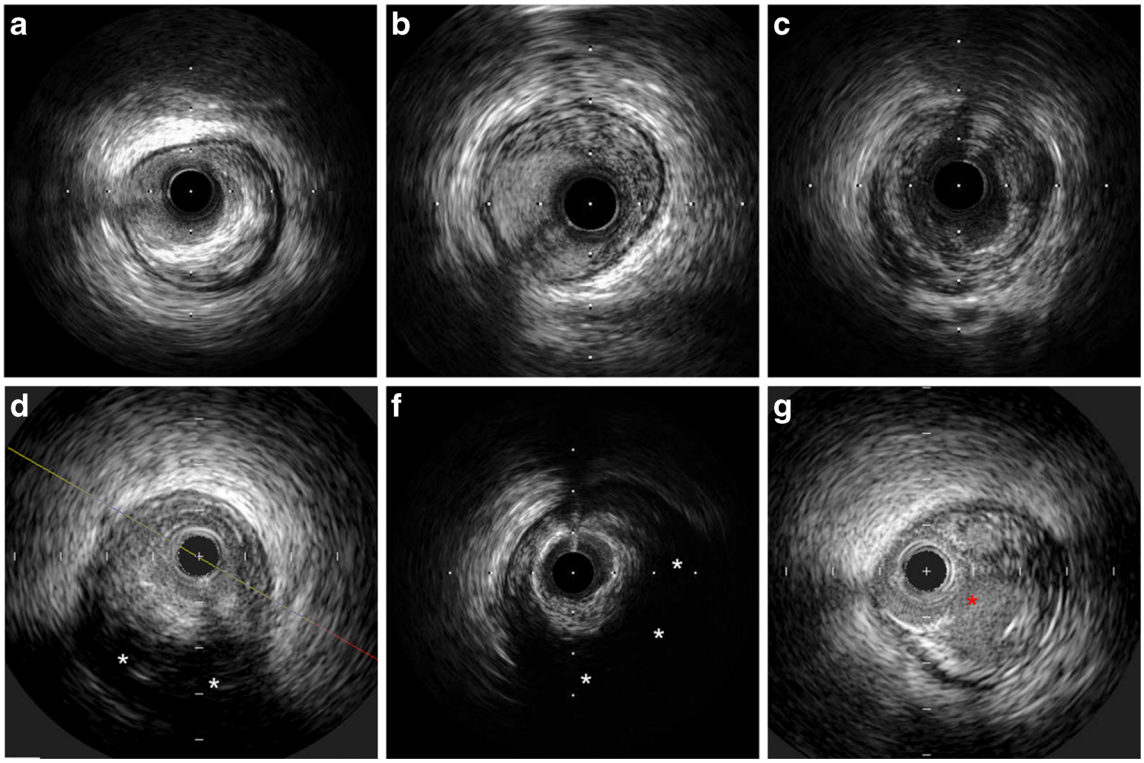

Fig. 1 Intravascular ultrasound plaque characteristics. **a** Highly echogenic plaque. **b**, **c** Echolucent plaques. **d**–**f** Attenuated plaque (*white asterisks*). **g** Plaque rupture with ruptured cavity (*red asterisk*)

undergoing PCI [45–47]. A recent meta-analysis of five clinical trials including 3833 patients showed that incidence of a thrombosis in MI (TIMI) score of 0–2 after PCI was significantly higher in patients with attenuated plaque (28.6%) than in those without attenuated plaque (5.8%) [48]. Endo et al. reported that peri-procedural no-reflow incidence was 18% in STEMI patients but was increased (up to 88%) in patients with long attenuated plaque (>5 mm) and plaque rupture [49]. A recent study demonstrated that large attenuated plaque with a maximal attenuation angle of ≥30° was related to unstable atherosclerotic plaque and predicted OCT-defined thin-cap fibroatheroma (sensitivity, 89%; specificity, 64%) and post-stenting peak CK-MB elevation [50].

Plaque Rupture

Plaque rupture is the most common type of plaque complication, accounting for 70% of AMIs [51, 52]. Studies have reported that IVUS-detected infarct-related plaque rupture in 16–56% of patients [53–56]. Hong et al. reported that IVUS detected plaque rupture in 66% of culprit lesions and 17% of non-infarct-related arteries in AMI patients [57]. Ruptured plaques cause symptoms in patients with small MLAs and thrombus formation, whereas silent plaque rupture is a form of wound healing that leads to lesion progression [58, 59]. Plaque ruptures without significant stenosis detected secondarily or incidentally at follow-up have not been shown to cause events. Plaque rupture is the most common cause of no-reflow and is associated with the worst clinical outcome [60–62]. Kusama et al. [63] showed that plaque rupture was associated with larger infarcts and a higher incidence of no-reflow after PCI. However, plaque rupture findings in IVUS do not always reflect the culprit lesion.

Thrombus

The IVUS hallmarks of thrombus (lobulated mass within the lumen, distinct interface between the presumed thrombus and underlying plaque, scintillating echoes, and blood flow within the thrombus) have limited sensitivity and specificity, and ruling out this diagnosis is only possible if all features are not present.

Positive and Negative Remodeling

Pathology and IVUS studies have demonstrated that coronary arteries are remodeled in response to plaque growth by expansion (positive remodeling) or constriction (negative remodeling) of the vessel wall [52, 64, 65]. Positive remodeling is regarded as compensatory enlargement to maintain coronary blood flow and is associated with a large lipid core, calcification, and macrophage infiltration, which might have a role in arterial cell matrix breakdown [66, 67]. Nakamura et al. [68] reported that among 125 symptomatic patients, positive remodeling at culprit lesions was found in 82% of those with

AMI, 78% of those with unstable angina, and 33% of those with stable angina. Negative remodeling is suggested to be a result of an advanced process of atherosclerosis leading to constricting adventitial fibrosis behind plaque [52, 65–67]. Compared with positive remodeling, negatively remodeled lesions are longer, more calcified, and more stenosed [69, 70]. Recently, the PROSTECT sub-study [71] showed that positive and negative remodeling was associated with major adverse cardiac events related to non-culprit lesions. In addition, positive remodeling was suggested to be a predictor of peri-procedural MI and no-reflow [72, 73].

Calcification

IVUS is a more accurate tool for detecting calcium than angiography (Fig. 2). In a study including 1155 native-vessel target lesions, IVUS detected calcium in 73% of lesions (vs. 38% by angiography) [74]. However, IVUS did not detect calcium in 14.8% of the segments with micro-calcium deposits or deep calcium hidden behind large necrotic cores [44]. Although calcium is more frequently detected in stable than in unstable lesions, spotty calcium and calcified nodules are likely to be associated with vulnerable lesions [61, 75]. Calcium has been shown to be related to acute procedural complications including bleeding, stent thrombosis, target vessel revascularization, and MI after revascularization [76–79]. Worse outcomes after PCI in calcified lesions can be explained by the following. First, stent underexpansion (an important predictor of restenosis and stent thrombosis) occurs frequently in calcified lesions. Second, using high-pressure balloon inflation and plaque modification devices in severely calcified lesions is associated with peri-procedural adverse events including no-reflow, dissection, and perforation [78]. Thus, IVUS is indispensable for plaque evaluation and stent optimization in calcified lesions.

Stent Sizing

Sizing with the IVUS reference lumen dimension is safe and effective, whereas use of mid-wall or media-to-media dimensions is more aggressive and requires more experience and caution. Although angiography does not always eliminate foreshortening projection, IVUS accurately measures lesion length during motorized pullback, regardless of bend points or a tortuous or foreshortened lesion. Reference segment identification and stent length selection with IVUS ensures that

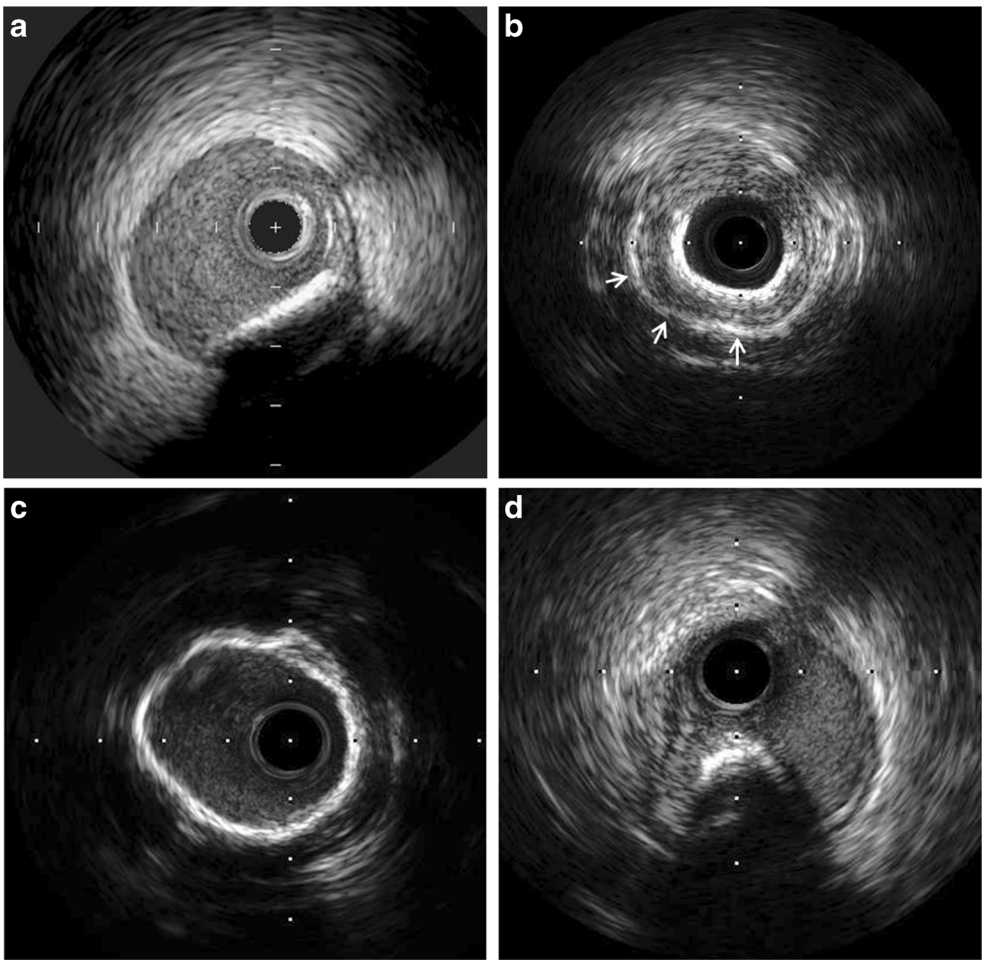

Fig. 2 IVUS-detected calcium. **a** Small superficial calcium. **b** Superficial calcification with reverberation artifact (*arrow*). **c** Superficial encircling calcium. **d** Calcified nodule

residual plaques at the proximal and distal ends of a stenosis will be completely covered by the stent (Fig. 3).

Stent Optimization

An optimally implanted stent has full and symmetrical expansion, complete stent–vessel wall apposition, no plaque prolapse, no dissections or other complications, and no residual edge plaque. IVUS-guided stent optimization is useful for minimizing mechanical problems that can lead to stent failure.

Expansion

The common causes of restenosis in both bare-metal stents (BMSs) and drug-eluting stents (DESs) are intimal hyperplasia and stent underexpansion. Stent underexpansion is correctable and preventable, so there has been a consistent effort to clarify the post-procedural minimal stent area (MSA) necessary to avoid restenosis. For preventing BMS restenosis, studies have reported a post-stenting MSA threshold of 6.4–6.5 mm^2 [80–82]. For first-generation stents, the post-procedural MSA cutoff was reported as 5.0–5.5 mm^2 with sirolimus-eluting stents (SESs) and 5.7 mm^2 in paclitaxel-eluting stents [80, 82–85]. For newer generation stents, Song et al. showed that the optimal cutoff post-stenting MSA values for preventing restenosis were similar between zotarolimus-eluting stents, everolimus-eluting stents, and SESs (5.3, 5.4, and 5.5 mm^2, respectively) (Table 2) [85].

Although stent optimization using an absolute MSA cutoff is practical and simple, various vessel sizes should be considered in real practice. In addition, an MSA of >5.0 mm^2 may not be achievable in small vessels where stent expansion represented as the MSA/reference lumen area may be a predictor of an adequate lumen at follow-up [84]. The SIRIUS trial reported that the MSA threshold for predicting an adequate follow-up MLA in small coronary arteries (reference vessel diameter <2.8 mm) was 4.5 mm^2 in SESs and 6 mm^2 in BMSs [82]. For newer-generation DESs, Song et al. suggested an MSA cutoff of 4.9 mm^2 in small vessel lesions with reference diameters of 2.5–3.0 mm [85].

To identify the MSA criteria for LMCA, Kang et al. [86•] evaluated 403 patients undergoing SES implantation in LMCA. Based on segmental analysis, the MSA cutoffs for predicting 9-month in-stent restenosis were 5.0 mm^2 for the left circumflex artery ostium, 6.3 mm^2 for the LAD ostium, 7.2 mm^2 for the polygon of confluence, and 8.2 mm^2 for the proximal LM, within the corresponding segments. Even in a two-stent group, lesions with complete expansion at all sites showed only a 6% restenosis rate; this was similar to that of a

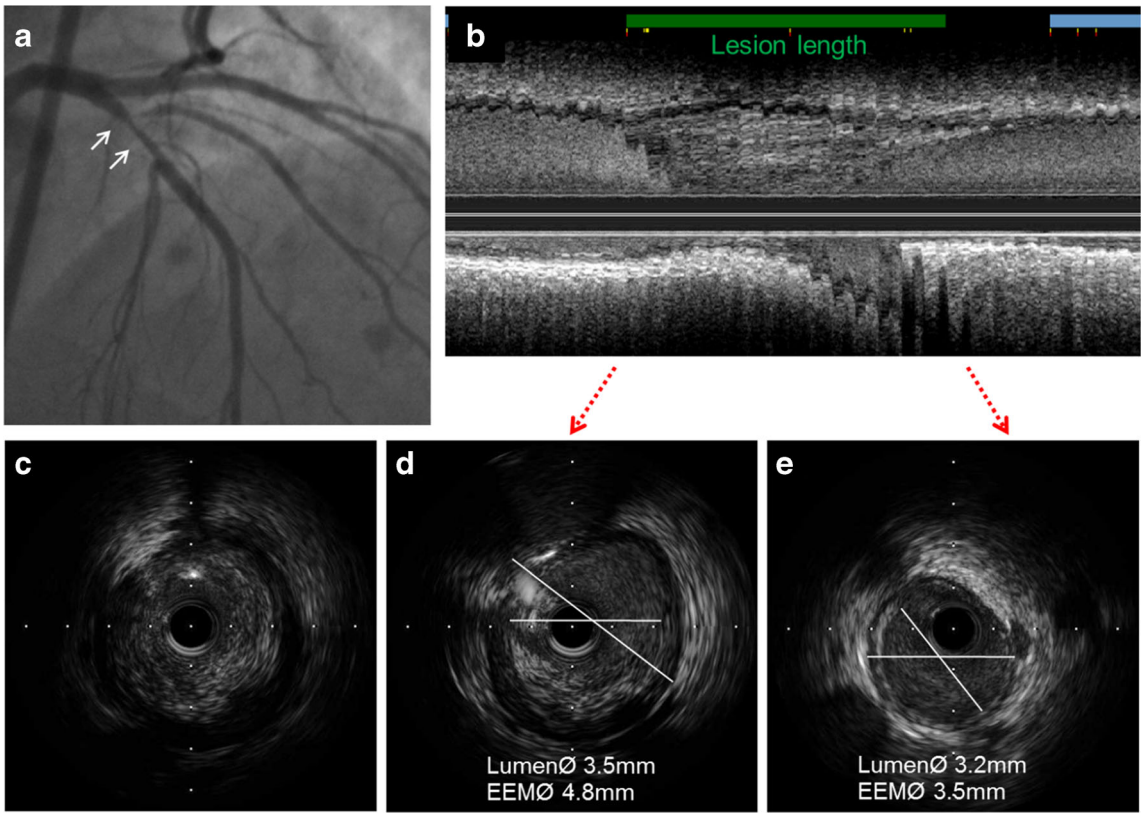

Fig. 3 Stent sizing by intravascular ultrasound. **a** Coronary stenosis (*arrows*) on angiography. **b** Intravascular ultrasound-measured lesion length using a longitudinal view. **c** A large plaque at the minimal lumen area site. **d** Measurement of lumen and vessel diameters at the proximal reference segment. **e** Measurement of lumen and vessel diameters at the distal reference segment

Table 2 Optimal IVUS criteria post-stenting to predict adverse outcomes

	Stent	Lesion no.	Endpoint (rate, %)		Duration (months)	Mean RVD/RLD (mm)	Post-stenting IVUS parameter	Cutoff		Sensitivity/specificity (%)
Morino et al. [81]	BMS	543	Target lesion revascularization	10.1	9	RVD 3.0	MSA	6.5 mm^2		PPV 17%, NPV 94%
Sonoda et al. [82]	BMS	50	MLA < 4 mm^2		8	RLD 2.8	MSA	6.5 mm^2		63/78
	SES	72				RLD 2.8		5.0 mm^2		76/83
Hong et al. [83]	SES	543	Angiographic ISR	3.9	6	RVD 3.0	MSA	5.5 mm^2		67/67
							Stent length	40 mm		81/78
Okumura et al. [84]	SES	169	Angiographic ISR	7.7	7	RVD 2.4	MSA	5.0 mm^2		77/72
							Stent length	30 mm		69/77
Doi et al. [80]	BMS	1098	Angiographic ISR	31	9	RVD 2.8	MSA	6.4 mm^2		c-statistics 0.64
	PES	482		10		RVD 2.8		5.7 mm^2		c-statistics 0.64
Song et al. [85]	SES	541	Angiographic ISR	3.3	9	RVD 2.9	MSA	5.5 mm^2		72/66
	ZES	220		4.5		RVD 3.3		5.3 mm^2		57/62
	EES	229		4.4		RVD 3.2		5.4 mm^2		60/60
Kang et al. [86•]	SES	403	Angiographic ISR	11.4	9		MSA	LM	8.2 mm^2	80/81
								POC	7.2 mm^2	100/78
								LAD os	6.3 mm^2	73/85
								LCS os	5.0 mm^2	78/78
Liu et al. [127]	BMS	255	Angiographic edge restenosis	2.4	9		Edge plaque burden	48%		c-statistics 0.70
	PES	276		5.2				47%		c-statistics 0.69
Morino et al. [138]	SES	162	Angiographic edge restenosis	4.1	8		Edge plaque burden	52%		80/82
Kang et al. [89•]	E-ZES	236	Angiographic edge restenosis	2.1	9		Edge plaque burden	55%		81/80
	R-ZES	246		2.8						
	EES	505		2.4						

MLA (mm^2) minimal lumen area, *RVD* (mm) reference vessel diameter, *RLD* (mm) reference lumen diameter, *LL* (mm) lesion length, *ISR* in-stent restenosis, *BMS* bare-metal stents, *SES* sirolimus-eluting stent, *PES* paclitaxel-eluting stents, *ZES* zotarolimus-eluting stents, *EES* everolimus-eluting stents

single stent group (6.3%) and non-bifurcation LMCA (4.5%) lesions. Furthermore, post-stenting underexpansion was an independent predictor of 2-year major adverse cardiac events (MACEs).

Residual Plaque Burden

Residual plaque burden is a predictor of late stent thrombosis and edge restenosis. Fujii et al. reported that the presence of a significant residual reference segment stenosis (defined as an edge lumen cross-sectional area of <4 mm^2 and a plaque burden of >70%) was more common in the stent thrombosis group compared with the matched control group (67 vs. 9%, $p < 0.001$) [87]. Okabe et al. suggested that DES patients who developed stent thrombosis had smaller MSAs, more residual disease at the stent edges and larger plaque burdens [88]. Kang et al. evaluated newer generation DESs and suggested that 9-month edge restenosis was predicted by a post-stenting reference segment plaque burden of approximately >55%, and that this could be used to determine the optimal landing site. In addition, the cutoff values of residual plaque burden were similar for the proximal and distal reference segments (56.4 and 51.9%, respectively) (Table 2) [89•]. Angiographic stenosis is poorly correlated with IVUS-measured plaque burden especially in reference segments, so IVUS is an indispensable tool for stent optimization in daily practice [90].

Acute Malapposition

Incomplete stent apposition is defined as the separation of stent struts from the arterial wall with evidence of blood flow behind the strut, where the strut does not cross a side-branch. Acute malapposition is a common finding; across several studies, the prevalence detected by IVUS was 11.5–25% in stable angina patients [91–94] and 34–40% in STEMI patients [95, 96]. There is little evidence suggesting an association between isolated acute malapposition and adverse outcomes. Most acute stent malapposition resolves over time and does not affect the incidence of stent thrombosis or in-stent restenosis. Guo et al. [97] reported that 40% of acute malapposition in STEMI patients was resolved at 1-year follow-up mainly due to negative remodeling. Hong et al. showed that post-procedure incomplete stent apposition occurred in 7.2% of DES-treated lesions and was not associated with MACEs or even an increased amount of intimal hyperplasia [98, 99]. Similarly, the ADAPT-DES IVUS sub-study showed acute malapposition in 12.6% lesions, but a very low rate of stent thrombosis (0.65%) [96]. Most studies have reported no significant relationship between acute malapposition and the occurrence of MACEs including stent thrombosis [92, 96, 97, 100, 101], and therefore, aggressive additional inflation to eliminate malapposition is unwarranted. Incomplete apposition is not a major concern as long as the stent is well expanded, and underexpansion should be corrected even if there is complete apposition. Large-scale prospective studies are needed to clarify the natural history and clinical impact of malapposition in the long term.

Edge Dissection

With an effort to achieve maximal acute gain during PCI, unexpected vessel dissection can occur at the transition between the rigid stent struts and the adjacent arterial wall at a site of compliance mismatch (Fig. 4) [116]. In one study, IVUS detected edge dissections after 9.2% of DES implantations. Residual plaque eccentricity, lumen-to-stent-edge-area ratio, and stent edge symmetry predicted coronary stent edge dissections, and dissections in less diseased reference segments more often evolved into intramural hematomas [102]. In a HORIZONS-AMI sub-study, significant stent edge dissection (more than medial dissection with a lumen area of <4 mm^2 or a dissection angle of ≥60°) was related to early stent thrombosis after primary PCI [101]. The ADAPT-DES IVUS sub-study reported that residual edge dissection was associated with target lesion revascularization at 1-year follow-up and suggested additional treatment with stents to produce a smaller effective

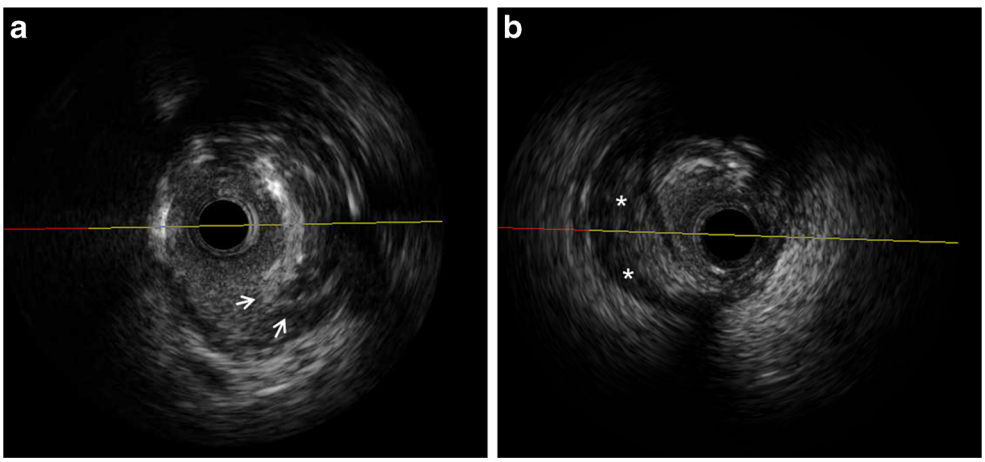

Fig. 4 Post-stenting edge complications. **a** Edge dissection (*arrows*). **b** Intramural hematoma within medial space (*asterisks*)

lumen area (<5.1 mm^2) [126]. Other studies have suggested the predictors of edge dissection as follows: calcified and lipid-rich plaques at the edges of stents, calcification angle, large plaque burden at stent edges, vessel over stretching, stent edge asymmetry, and residual plaque eccentricity [102–105]. In a current guideline, it is recommended that persistent and high-grade dissection with flow limitation in angiography is treated with prolonged balloon inflation or deployment of a second stent [3]. Conversely, non-flow-limiting minor dissections do not appear to impact on long-term clinical outcomes unless they result in lumen compromise. Low-grade and angiographically silent edge dissections may not be associated with adverse events [116–118, 121, 125]. However, some studies have reported a link between edge dissection and adverse clinical outcomes [85, 126, 127].

Intramural Hematoma

As a variant of dissection, intramural hematoma begins as a dissection of the media and propagates along the medial plane into more normal arterial segments without re-entering the lumen [106]. Blood accumulates in the medial space, the EEM expands outward, and the internal elastic membrane is pushed inward to cause lumen compromise. When contrast accumulates within the split media, echolucent contrast can be seen within the echogenic blood. Maehara et al. reported that the incidence of intramural hematomas detected by IVUS was 6.7% after stenting with BMSs [107] and Liu et al. reported the incidence as 3.2% after stenting with DESs [102]. Among IVUS-identified hematomas, 29% were not detected by angiography and 11% appeared as new angiographic stenosis. Moreover, intramural hematoma was associated with a high rate of MI, need for repeat revascularization, and sudden death. Therefore, IVUS has a pivotal role in detecting edge complications and helps with making clinical decisions.

Tissue Protrusion

In the HORIZONS-AMI sub-study, significant tissue protrusion with a lumen area of <4 mm^2 was more prevalent in patients with early stent thrombosis after primary PCI [108]. In another study, tissue protrusion was associated with more stent thrombosis and no-reflow in patients with AMI, but was not associated with worse long-term outcomes after stent implantation for infarct-related arteries [109].

Clinical Impact of IVUS-Guided DES Implantation

While early randomized trials with DESs failed to prove superior clinical outcomes in IVUS-guided PCI [110–112], recent large-scale registries, randomized trials, and meta-analyses showed that IVUS guidance was associated with a lower rate of MACEs and of the hard endpoints of cardiovascular mortality, MI, and stent thrombosis (ST), compared with angiography-guided PCI [113–118]. In the sub-study of ADAPT-DES [119•], the largest prospective registry of 8583 patients (39% of patients treated with IVUS-guided PCI), the IVUS-guided group had lower rates of ST (0.6 vs. 1.0%), MI (2.5 vs. 3.7%), and MACEs (3.1 vs. 4.7%) at 1-year follow-up compared with the angiography-guided group, particularly in patients with acute coronary syndrome and complex lesions.

Table 3 summarizes randomized clinical trials comparing the clinical impact of IVUS- and angiography-guided PCI in the DES era [110–112, 116, 120–122]. A recent randomized multicenter trial, the Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions (IVUS-XPL), evaluated 1400 patients with long coronary lesions (≥28 mm in stent length). This study proved that IVUS guidance was superior to angiography guidance in terms of improving long-term clinical outcomes [116]. IVUS-guided everolimus-eluting stent implantation significantly reduced the rate of 1-year MACEs (2.9 vs. 5.8%), which was mainly driven by a lower risk of target lesion revascularization (2.5 vs. 5.0%). In a meta-analysis conducted by Elgendy et al., IVUS-guided PCI was beneficial in reducing the rates of MACEs (6.5 vs.10.3%), ischemia-driven target lesion revascularization (4.1 vs. 6.6%), cardiac death (0.5 vs.1.2%), and stent thrombosis (0.6 vs.1.3%) compared with angiography-guided PCI [113]. Zhang et al. conducted a meta-analysis of 29,068 patients undergoing DES implantation and emphasized the benefit of IVUS guidance in reducing ST and MACEs [118].

In lesions with chronic total occlusion (CTO), IVUS can help resolve proximal cap ambiguity by identifying the position of the main branch and clarifying the guidewire position (in true or false lumens) during both antegrade and retrograde CTO crossing attempts. The AIR-CTO randomized controlled trials showed comparable rates of clinical events between IVUS- and angiography-guided PCI [112], whereas the prospective, randomized, multicenter CTO-IVUS trial showed a reduction in 1-year MACE rate after new-generation DES implantation with IVUS guidance [121].

A subgroup analysis from the MAIN-COMPARE registry showed that the 3-year mortality rate was reduced with IVUS compared with angiography guidance (6.3 vs. 13.6%) during LMCA stenting. In particular, the 3-year mortality rates for the 145 matched pairs of patients undergoing DES implantation were significantly lower with IVUS than with angiography guidance (4.7 vs. 16.0%) [123].

Even in the era of DESs, most studies have validated the superiority of IVUS-guided PCI (vs. angiography-guided PCI) to improve clinical outcomes [80–83, 85, 86•, 87, 89•, 101, 108, 124–130] by minimizing underexpansion and geographic miss and by treating PCI complications. In the ADAPT-DES study, longer stent lengths, higher inflation

Table 3 Randomized clinical trials (RCT) and meta-analysis comparing IVUS- versus angiography-guided DES implantation

	RCT							Meta-analysis of RCT	
	(1) IVUS-XPL [116]	(2) Tan et al. [112].	(3) CTO-IVUS [121]	(4) AIR-CTO [112]	(5) RESET [111]	(6) AVIO [110]	(7) HOME DES [120]	Elgendy et al. [113] (1)–(7)	Shin et al. [114•] (1,3,5)
Patients	700/700	61/62	201/201	115/115	269/274	142/142	105/105	1593/1599	1170/1175
DES type	2nd generation	1st generation	2nd generation	1st and 2nd generation	2nd generation	1st generation	1st generation	1st and 2nd generation	2nd generation
Duration (Mo)	12	24	12	24	12	24	18		12
Angiographic character									
CTO (%)	NR	0/0	100/100	100/100	0/0	14/18	NR		
LL (mm)	35/35	NR	36/36	28/29	30/30	27/26	18/18		
Clinical outcome									
Primary end point	MACE	MACE	MACE	In-stent late lumen loss	MACE	Post-stenting MLD	MACE	MACE	MACE
Definition of MACE	Cardiac death, AMI, ID-TLR	Death, non-fatal MI, TLR	Cardiac death	NR	Cardiac death, MI, ST, TVR	Cardiac death, MI, TVR	Death, MI, TLR	Death, MI, TLR,TVR, ST	Cardiac death, MI, ST
MACE	0.48 (0.28, 0.83) $p = 0.007$	0.42 (0.17, 1.00) $p = 0.031$	0.35 (0.13, 0.97) $p = 0.035$	0.82 (0.45, 1.52) $p = 0.641$	0.59 (0.28, 1.24) $p = 0.16$	0.73 (0.41, 1.26) p = ns	0.91 (0.38, 2.15) p = ns	0.60 (0.46, 0.77) $p < 0.0001$	0.36 (0.13, 0.99) $p = 0.040$
Cardiac mortality	0.60 (0.14, 2.52) $p = 0.48$	0.67 (0.11, 4.00) $p = 0.648$	NC	0.60 (0.15, 2.44) $p = 0.557$	NC	0.12(0.01, 4.00) p = ns	NR	0.46 (0.21, 1.00) $p = 0.05$	0.38 (0.10, 1.42) $p = 0.134$
MI	0.14 (0.00, 6.82) $p = 0.32$	0.52 (0.05, 5.06) $p = 0.578$	NC	1.33 (0.80, 2.20) $p = 0.463$	NC	0.83 (0.32, 2.13) p = ns	0.29 (0.05, 1.73) p = ns	0.52 (0.26, 1.02) $p = 0.06$	NC
TLR	0.51 (0.28, 0.91) $p = 0.02$	0.39 (0.14, 1.10) $p = 0.045$	0.62 (0.20, 1.89) $p = 0.40$	0.65 (0.26, 1.61) $p = 0.484$	NR	0.76 (0.34, 1.66) p = ns	1.00 (0.31, 3.20) p = NS	0.60 (0.43, 0.84) $p = 0.003$	0.61 (0.40, 0.93) $p = 0.020$
TVR	NR	NR	0.48 (0.17, 1.42) $p = 0.66$	0.64 (0.31, 1.33) $p = 0.383$	0.66 (0.31, 1.41) $p = 0.28$	0.59 (0.29, 1.21) p = ns	NR	0.61 (0.41, 0.91) $p = 0.02$	NR
ST	1.00 (0.14, 7.10) $p > 0.99$	0.52 (0.05, 5.06)	NC	0.14 (0.01, 1.99) $p = 0.162$	NC	3.00 (0.12, 74.00) p = ns	0.66 (0.19, 2.34) p = ns	0.49 (0.24, 0.99) $p = 0.04$	0.50 (0.13, 2.01) $p = 0.320$

Data are presented as IVUS guidance/angiography guidance

NR not reported, *NC* not calculable because of nonoccurrence of the events, *DES* drug-eluting stent, *ACS* acute coronary syndrome, *LMCA* left main coronary artery, *LAD* left anterior descending artery, *CTO* chronic total occlusion, *RVD* reference vessel diameter, *LL* lesion length, *MACE* major adverse clinical events, *TLR* target lesion revascularization, *TVR* target vessel revascularization, *ST* stent thrombosis

pressure, frequent post-dilatation, and larger stent sizes/balloons were used in the IVUS-guided group [119•]. Previous meta-analyses also reported a larger stent size and minimal lumen diameter in the IVUS-guided group (vs. the angiography-guided group) and supported the recommendation to expand the routine use of IVUS guidance [113, 117].

A recent economic analysis showed that IVUS-guided PCI is cost-effective especially in high-risk patients with diabetes, renal insufficiency, and acute coronary syndrome [131]. The incremental cost-effectiveness ratio remained lower than the implicit willingness-to-pay threshold at 1 year, and a negative incremental cost-effectiveness ratio was produced when the IVUS benefit covered full life expectancy. Further randomized trials with cost-effectiveness analyses are necessary to evaluate clinical and cost efficacy of IVUS-guided PCI in routine practice.

Assessment of Stent Failure

IVUS provides insight into the precise mechanisms of in-stent restenosis by giving detailed information about stent underexpansion, the extent and distribution of intimal tissue, plaque progression at the edges of stents, and vascular remodeling (Fig. 5). In a study evaluating lesions with DESs and in-stent restenosis, underexpansion (minimal stent area <5 mm^2) and significant intimal hyperplasia (intimal area >50% of stent) were seen in 42 and 93%, respectively [132]. Although intimal hyperplasia is the predominant mechanism of in-stent restenosis, interventionists should focus on correction of stent underexpansion as a preventative mechanism during the procedure. A larger stent can provide more room for future intimal growth, so IVUS guidance may be helpful to avoid underexpansion especially in long lesions, small vessels, and other complex lesions. There is emerging evidence suggesting that chronic inflammation and/or incompetent endothelial function induces in-stent neoatherosclerosis, which is an important mechanism of in-stent restenosis and stent thrombosis in the late phase [133–136]. IVUS-documented causes of very late stent thrombosis have included in-stent plaque rupture, presumably the consequence of in-stent vulnerable neointima, another manifestation of in-stent neoatherosclerosis [137]. Although the low resolution of IVUS limits identifying macrophage and lipid infiltration within neointima, in-stent intimal rupture and calcified neointima may suggest the presence of advanced neoatherosclerosis.

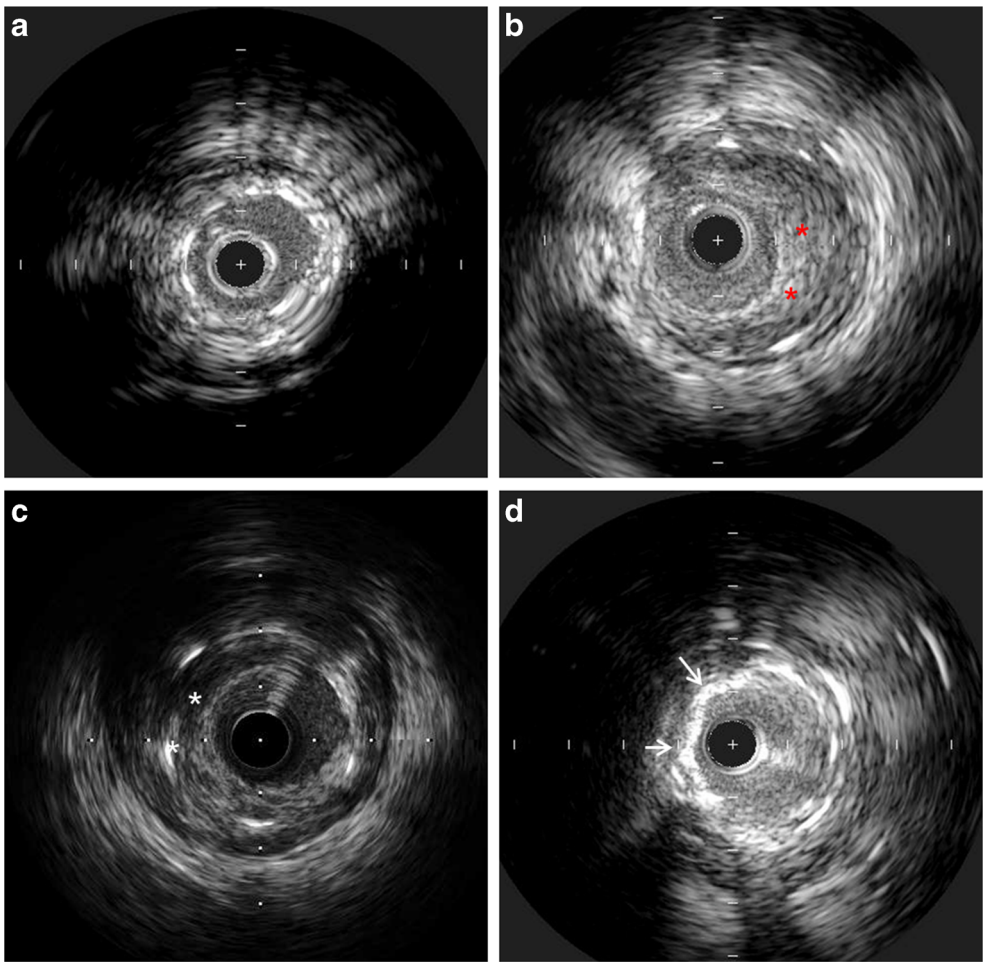

Fig. 5 Intravascular ultrasound mechanism of visualizing in-stent restenosis. **a** Stent underexpansion. **b** Intimal hyperplasia with echogenic neointima (*red asterisks*). **c** In-stent echolucent neointima (*white asterisks*). **d** Calcified neointima (*arrows*) inside stent

Conclusion

For planning treatment strategies, IVUS provides valuable information about lesion severity, lumen and vessel size, lesion length, and plaque characteristics. By determining appropriate stent sizes and optimizing stenting procedures, IVUS-guided PCI improves clinical outcomes especially in patients with high-risk coronary lesions.

Compliance with Ethical Standards

Conflict of Interest Both authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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