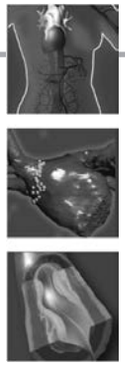

Intravascular ultrasound guidance for percutaneous coronary intervention in the current practice era

Coronary angiogram, considered the gold standard for coronary assessment, consistently underestimates vessel size/lesion severity and usually misses heavily calcified plaques. Intravascular ultrasound (IVUS) technology accurately determines vessel size/lesion severity and allows a detailed plaque composition evaluation. The role of IVUS guidance after stent implantation has been explored in various trials; however, limited data are available on how the preprocedural use of IVUS might impact the intervention strategy and clinical outcome. Based on the latest published evidence and in our own experience, we support a more liberal use of IVUS, especially when approaching complex coronary lesions, thereby resulting in an optimal interventional result that might affect clinical outcome.

KEYWORDS: intravascular ultrasound ■ percutaneous coronary intervention ■ stenosis

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Intravascular ultrasound (IVUS) is an invasive imaging modality used to visualize coronary cross-sectional anatomy. IVUS technology has been proven to be superior to coronary angiography for assessment of vessel size, plaque composition, calcium content and lesion severity [1–3]. The role of IVUS guidance after stent implantation has been previously explored; however, limited information is available on how the preprocedural use of IVUS might impact the intervention strategy and clinical outcome, particularly when approaching complex coronary lesions. We believe that IVUS provides additional information beyond angiography, often leading to more optimal results and improving the outcome after percutaneous coronary intervention (PCI). Given the continuous expansion of PCI for treating sicker patients and more complex coronary lesions, we believe that IVUS plays a central role in the current practice era. In this article, we examine the role of IVUS guidance for PCI in the current practice era in view of the latest clinical evidence.

Basic measurements

Normal coronary arteries usually have three layers on IVUS that correspond with the histologic structure: the innermost echogenic layer (intima-internal elastic membrane), the echolucent muscle layer (media) and the outer echogenic stratum (external elastic membrane [EEM]–adventitia) (Figure 1). From a practical point of view, most IVUS measurements are based on the lumen (interface between blood flow and the leading edge of the intima) and EEM (interface between the media and the adventitia) definition (Figure 2). Subsequent to the estimation of the proximal and distal reference diameters (largest lumen within the same segment and 10 mm proximal or distal to the stenosis, respectively), the derived measurements are established (Table 1). In addition, stents require evaluation of the strut apposition and expansion. Good apposition is defined as close contact in order to preclude blood flow between any strut and the underlying wall. Appropriate stent expansion is defined as a symmetrically expanded stent, with circular lumen, not smaller than the proximal and/or distal reference lumen. For previously placed stents, neointimal hyperplasia should be adequately recognized, usually detected as very low echogenic tissue in early in-stent restenosis (ISR) and as more echogenic in late ISR. Stent evaluation (and struts apposition) requires avoidance of numerous artifacts due to the probe angulation [4]. A detailed description of standards for IVUS acquisition and measurements is reported in the American College of Cardiology (ACC) consensus expert document [5].

Evaluation of intermediate coronary lesions

Intermediate coronary lesions identified by angiography (40–70% angiographic stenosis) represent a challenge when making revascularization decisions. Coronary angiography, considered the standard for coronary evaluation, consistently and significantly underestimates lumen diameter when compared with IVUS measurements (Figure 3) [1,6,7]. Angiographic underestimation of lumen size can lead to undersized devices and higher rates of major cardiac events on short- and

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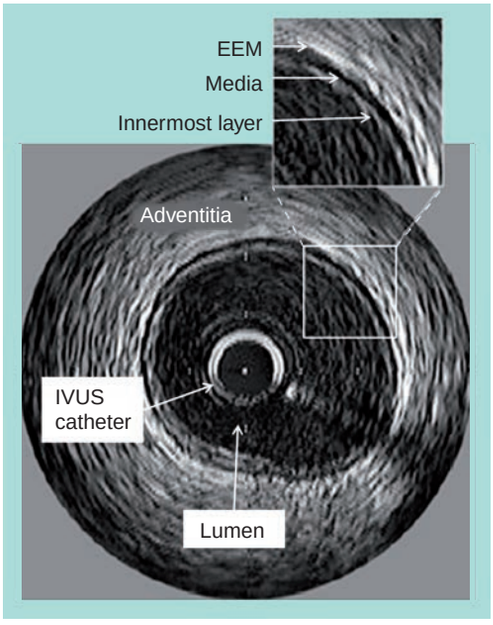

Figure 1. Normal coronary artery showing the innermost layer, the media layer and the external elastic membrane. The EEM is recognized as the interface between the echolucent muscular-media and the adventitia. EEM: External elastic membrane; IVUS: Intravascular ultrasound.

long-term outcomes after PCI [8–10]. Intermediate coronary lesions are evaluated either anatomically by assessing the stenosis severity using IVUS or physiologically by measuring the hemodynamic significance of a lesion using the coronary pressure wire-derived fractional flow reserve (FFR) or the Doppler wire-derived coronary flow reserve (CFR). Although anatomic evaluation does not provide direct estimation of the hemodynamic significance of a coronary lesion, several studies have demonstrated a good correlation between IVUS and nuclear perfusion imaging [11], CFR [12] and FFR [13,14]. Takagi *et al.*, when correlating 51 lesions with both IVUS and FFR (mean reference lumen area: 9.26 ± 2.72 mm^2) determined that a combination of a minimal lumen area (MLA) less than 3.0 mm^2 and a percentage area stenosis over 60% without exception met with a FFR under 0.75 [13]. In addition, Briguori *et al.*, when evaluating 53 lesions using IVUS and FFR (mean reference lumen area: 13.0 ± 6.1 mm^2), identified, by receiver operating characteristic curve analysis, that a large percentage area stenosis over 70%, a MLA under 4.0 mm^2, a minimal lumen diameter (MLD) under 1.8 mm and a lesion length over 10 mm to be the best cutoff values to fit with a FFR under 0.75 [14]. Nonetheless, this correlation seems to be less predictable in small coronary vessels [15,16].

Relevant clinical studies have validated FFR data by showing that deferring interventions in lesions with intermediate severity considered not hemodynamically significant (FFR >0.75 – 0.8) have favorable clinical prognosis [17–19]. Similarly, Abizaid *et al.* reported the clinical outcomes of 300 patients (357 intermediate native artery lesions) in whom intervention was deferred based on IVUS findings [20]. The only independent predictors of the 1-year composite of death/myocardial infarction (MI)/target lesion revascularization (TLR) were MLA and area stenosis before intervention measured by IVUS. In 248 lesions with a MLA over 4.0 mm^2, the rate of the composite end points was only 4.4%, driven primary by TLR (2.8%) (Figure 4). As a result, IVUS imaging is an acceptable alternative to physiological assessment in patients presenting with intermediate coronary lesions [20]. The lack of randomized clinical trials comparing FFR and IVUS does not allow us to conclude superiority of any of these technologies on clinical outcome.

In our clinical practice, we generally proceed as follows: in the presence of atypical symptoms or equivocal noninvasive ischemia test results, we prefer an initial evaluation using FFR, which is a well-validated strategy to confirm or negate the presence of ischemia. If morphologic information appears to be valuable for making a revascularization decision, IVUS is preferred. As a general rule, we use a MLA under 4.0 mm^2 and a percentage area stenosis greater than 70% as cutoff values for revascularization decisions on large vessels (reference vessel diameter >3.0 mm) based on IVUS dimensions in nonleft main locations. For left main position we use MLA under 6.0 mm^2 and percentage area stenosis over 70% (see left main-dedicated section). Nonetheless, if PCI is performed, IVUS provides additional information that allows for PCI optimization. However, IVUS and FFR should be understood as complementary techniques that provide valuable and different information. Independent of the selected technique or the specific technique available onsite, we encourage every catheterization laboratory to have an algorithm for decision making when approaching angiographically intermediate lesions. Nevertheless, ideally IVUS and FFR should be available as complementary tools.

Routine IVUS guidance for PCI

Results from the Angiography Versus Intravascular Ultrasound-Direct Stent Placement (AVID), the Thrombocyte Activity Evaluation and Effects of Ultrasound Guidance in Long Intracoronary Stent Placement (TULIP) and the Strategy for

Intracoronary Ultrasound-Guided PTCA and Stenting (SIPS) randomized clinical trials have demonstrated that routine IVUS guidance compared with angiography guidance for bare metal stent (BMS) placement decreases the rate of target vessel revascularization (TVR) by optimizing the stent features after deployment [6,21,22]. By contrast, other randomized trials have reported a neutral effect of IVUS guidance, namely the Restenosis after IVUS-guided Stenting (RESIST) and the Optimization with ICUS to Reduce Restenosis (OPTICUS) trials [23,24]. In addition, IVUS cost–effectiveness analysis after BMS implantation have demonstrated improvement event-free survival and identical cost at 2-year follow-up, suggesting that IVUS strategy was less expensive and more effective [25]. After the introduction of drug-eluting stents (DES) and the continual decreases in the rates of ISR, it has been suggested that the benefit of IVUS guidance may be minimized [26]. Nevertheless, DES underexpansion has been reported as an important predictor for further stent failure and stent thrombosis (ST) [8–10], issues of major concern after DES implantation [27]. However, limited data are available on how the preprocedural use of IVUS might modify the intervention strategy, particularly when approaching complex coronary lesions, such as left main coronary artery (LMCA) stenosis, ostial lesions of a large vessel, bifurcated lesions involving a large branch, undilatable lesions (heavy calcified plaques), degenerated saphenous vein grafts (SVGs) or diffuse ISR. In addition, no information is available on how IVUS guidance may impact the outcomes for these particular situations. Interestingly, Roy *et al*. reported for first time in a retrospective propensity score matched population the potential benefit of routine IVUS-guided implantation of DES, showing a significant decrease in the rate of acute ST [28]. In addition, the recent results from the Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE) registry demonstrated a significant benefit when routinely using IVUS for left main stenting [29]. Therefore, we recommend routine pre- and postintervention IVUS guidance each time a complex coronary lesion is approached.

Preintervention IVUS guidance

Intravascular ultrasound allows a precise assessment of the diseased segment to be intervened upon, adding significant information over that obtained by angiography [1,3], including details of plaque composition, and reference vessel size and lesion length. All these parameters have a crucial significance for planning the intervention strategy, selection of devices and prevention of complications.

■ Sizing & choosing the interventional devices

Since few clinical data are available on IVUS-guided device selection, our recommendations are based mostly on experience and represent our current clinical practice. Only one clinical trial, the Clinical Outcomes Ultrasound Trial (CLOUT), reported the safety of IVUS guidance when selecting a balloon size using the 'midwall' measurement (halfway between the lumen and EEM) [30]. We propose that the appropriate strategy and device size should be initially based on plaque composition and vessel size. Soft plaques – plaque tissue showing an echogenicity lower than the adventitia (hypoechoic) on IVUS, typically without calcium/fibrous – especially with large positive remodeling, present poorer outcomes after PCI, including higher rates of TLR independent of final minimal in-stent dimension, using either BMS or DES [31,32]. In addition, necrotic core volume detected

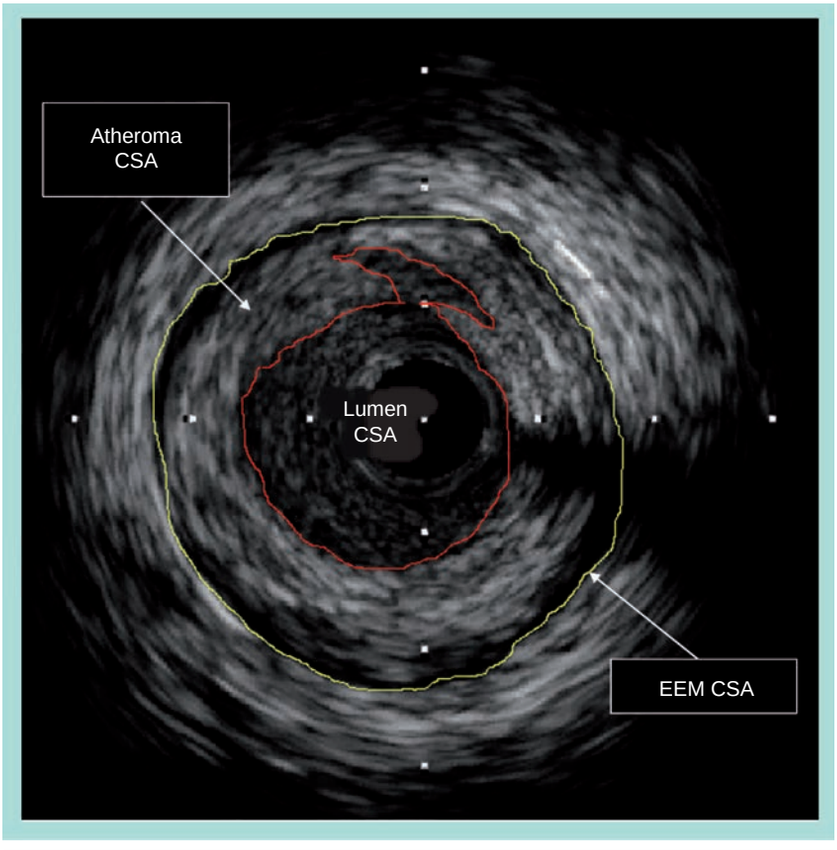

Figure 2. Basic intravascular ultrasound measurements of a coronary artery with atherosclerotic disease.
CSA: Cross-sectional area; EEM: External elastic membrane.

Table 1. Standard derived intracoronary ultrasound measurements.

Measurement	Definition
Lumen CSA	Area bounded by the luminal border
Minimum diameter	Shortest diameter through the center point of the lumen
Lumen area stenosis	(Reference lumen CSA – minimum lumen CSA)/reference lumen CSA
Plaque + media (or atheroma) CSA	EEM CSA – lumen CSA
Plaque (or atheroma) burden	(Plaque + media CSA)/EEM CSA
Stent CSA	Area bounded by the stent border

CSA: Cross-sectional area; EEM: External elastic membrane.

by using virtual histology (VH) IVUS correlates with the risk prediction of peri-interventional myocardial injury and presumably distal embolization after primary stent deployment in acute MI and stable patients [33,34]. It is our opinion that soft plaques, especially those with a large plaque burden or necrotic core, should be stented directly without prior balloon dilatation since they

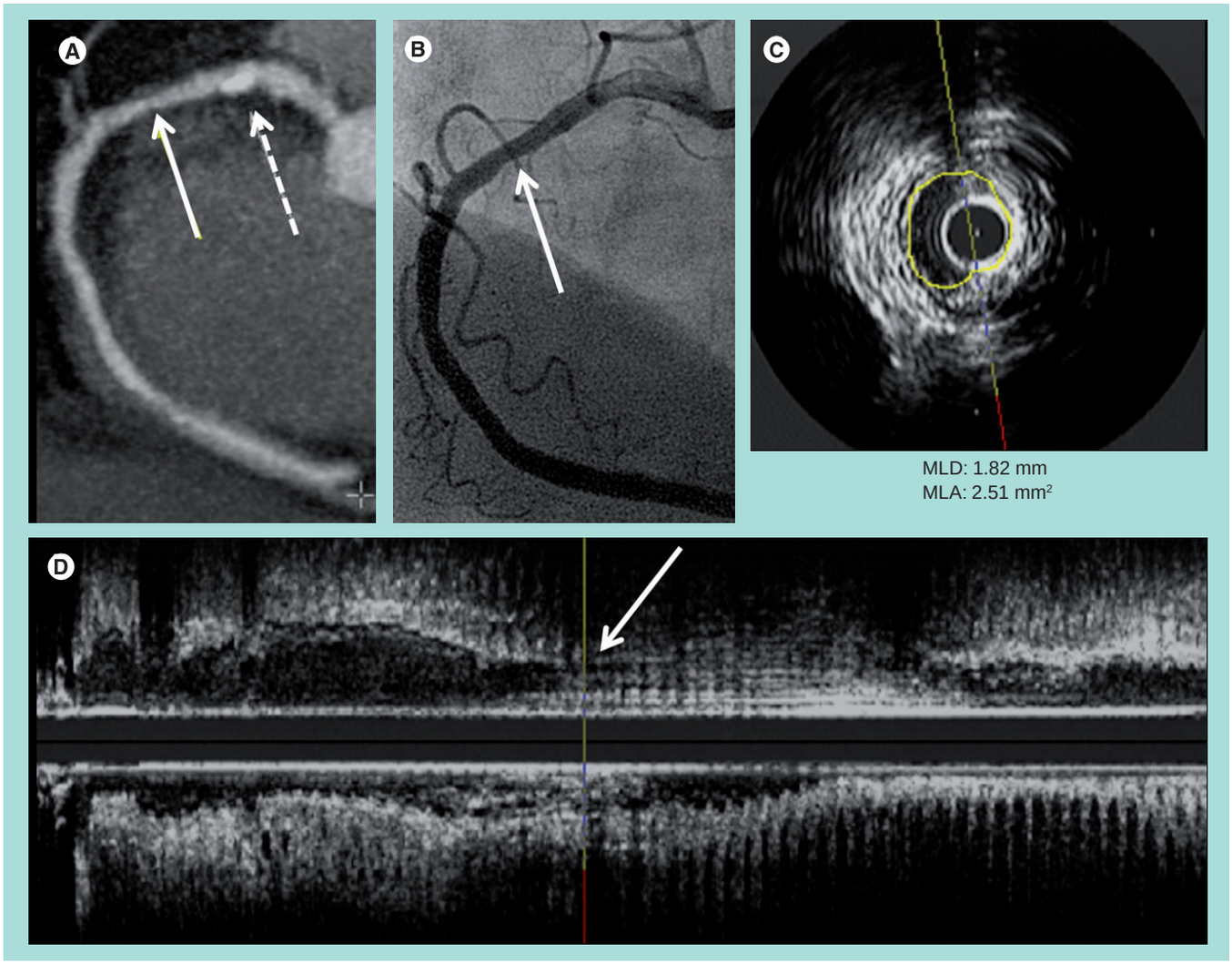

Figure 3. Angiographic underestimated lesion severity compared with intravascular ultrasound and computed tomography angiogram. (A) Multiplanar cardiac CT reconstruction showing the presence of a moderate stenosis caused by a noncalcified plaque (full arrow) and a more proximal severe calcified lesion (dashed arrow) involving the proximal right coronary artery. **(B)** Angiography of the same vessel showing the presence of a 30% stenotic lesion in the proximal RCA. **(C)** Cross-sectional intravascular ultrasound view of the pointed lesion (full arrows in **[A, B & D]**) showing the presence of a mixed plaque that determines a severe stenotic lesion. **(D)** Long intravascular ultrasound run view of the RCA.
MLA: Minimal lumen area; MLD: Minimal lumen diameter.

are easily dilatable lesions and prior manipulation may increase the risk of distal embolization and postprocedural MI [35]. Severe fibrotic lesions require dilatation before stenting using either a noncompliant balloon or cutting balloon sized just under the vessel diameter at the lesion site or sized similar to the reference lumen diameter. Severely calcified lesions without concentric arcs of calcium can be predilated with noncompliant balloons to evaluate the dilatability of the lesion. Severely calcified lesions with concentric calcification (360°) are the hallmark of undilatable lesions and in our experience require rotablator prior to stenting. The 'bigger is better' strategy also applies to DES, although the MLA required for minimal restenosis is smaller than the area required for BMS [36–38]. In addition, a larger stent cross-sectional area (CSA) has been linked to lower ST rates [39]. We therefore suggest choosing the stent size according to the true vessel size (slightly smaller than the EEM diameter at the lesion site and the proximal and distal reference segments). However, excessively dilated native vessels or SVGs, as well as a large mismatch between the proximal and distal diameters, are important exceptions that will require a different approach that avoids aggressive device sizing. In the case of diffuse disease, the CLOUT criteria could be used; the average of the lumen and EEM diameters at the least diseased segment [30]. Regarding the selection of stent length, some important considerations must be mentioned. However, in the current practice era, there is a more liberal use of longer stents, and some authors have suggested that the entire lesion should be covered by a DES to avoid edge residual stenosis [26]. A more current approach calls for 'spot stenting' of the critical stenosis, leaving the segments with intermediate disease without stent coverage. Katritsis *et al.* randomized 130 patients with long lesions to 'spot stenting' or long stents, and showed a clear advantage of the 'spot stenting' strategy as long as the plaque burden at the edges is under 50% [40]. In addition, much evidence supports the use of shorter DES. The rate of edge restenosis has been reported infrequently in DES randomized clinical trials [41], longer stents have been associated with a greater risk of ST and restenosis after DES implantation [42] and the use of 'full metal jacket' coverage has been linked with higher rates of adverse events [43] and precludes further surgical access to the vessel.

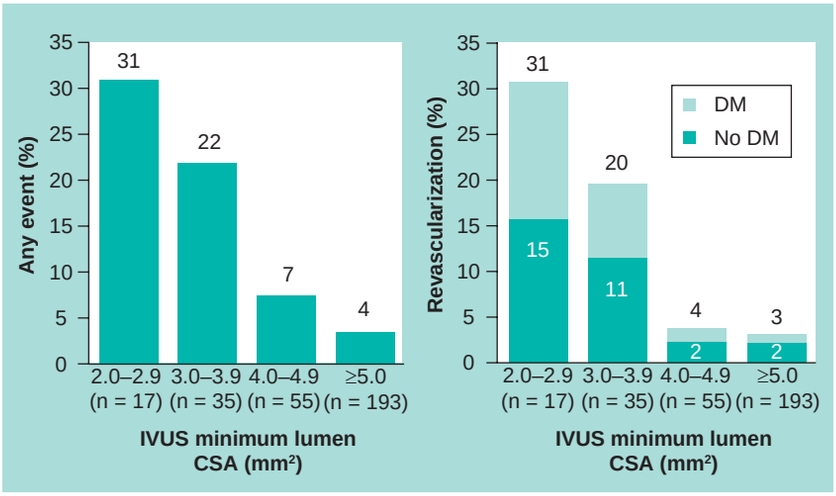

Figure 4. Clinical outcomes based on cross-sectional area to defer coronary interventions. The occurrence of any event (death, myocardial infarction or revascularization) decreased with increasing minimum lumen CSA. Target lesion revascularization decreased with increasing minimum lumen CSA, but it was lower in nondiabetic than diabetic patients.
CSA: Cross-sectional area; DM: Diabetes mellitus; IVUS: Intravascular ultrasound.
Adapted from [20].

■ Left main coronary disease

Left main coronary artery lesions are difficult to assess and characterize by angiography [44]. Often, the presence of contrast in the aortic cusp does not allow a direct visualization of the LMCA ostium [45]. In addition, the difficult appraisal of LMCA bifurcation or trifurcation or the lack of a normal reference segment make angiographic interpretation inaccurate [45]. Therefore, the reliability of quantitative coronary angiography on the LMCA is worse than in other coronary territories [46]. For those reasons, IVUS appears to be a very useful tool for accurate assessment of the LMCA when the angiographic interpretation is ambiguous (Figure 5). Indeed, the MAIN-COMPARE registry reported that IVUS-guided stenting may reduce long-term mortality compared with conventional angiography-guided stenting for unprotected LMCA stenosis [29]. In particular, in 145 matched pairs of patients receiving DES, the 3-year incidence of mortality was lower with IVUS guidance compared with angiography guidance (4.7 vs 16.0%; log rank p = 0.048) [29].

From a technical point of view, a good quality assessment of the LMCA requires the IVUS probe to be placed distally in the straighter vessel, usually the left anterior descending artery (LAD), and the guiding catheter to be disengaged to avoid missing the ostium during pullback [5]. In addition, the selection of an appropriate guiding catheter to permit a coaxial imaging is another crucial point. Clinical studies support that a MLD under 2.8 mm and/or a MLA under 5.9 mm^2 predict hemodynamically significant LMCA lesions, with sensitivity and specificity above 90% [47] and an adequate correlation with long-term clinical outcome as well [48]. In our practice, an MLA

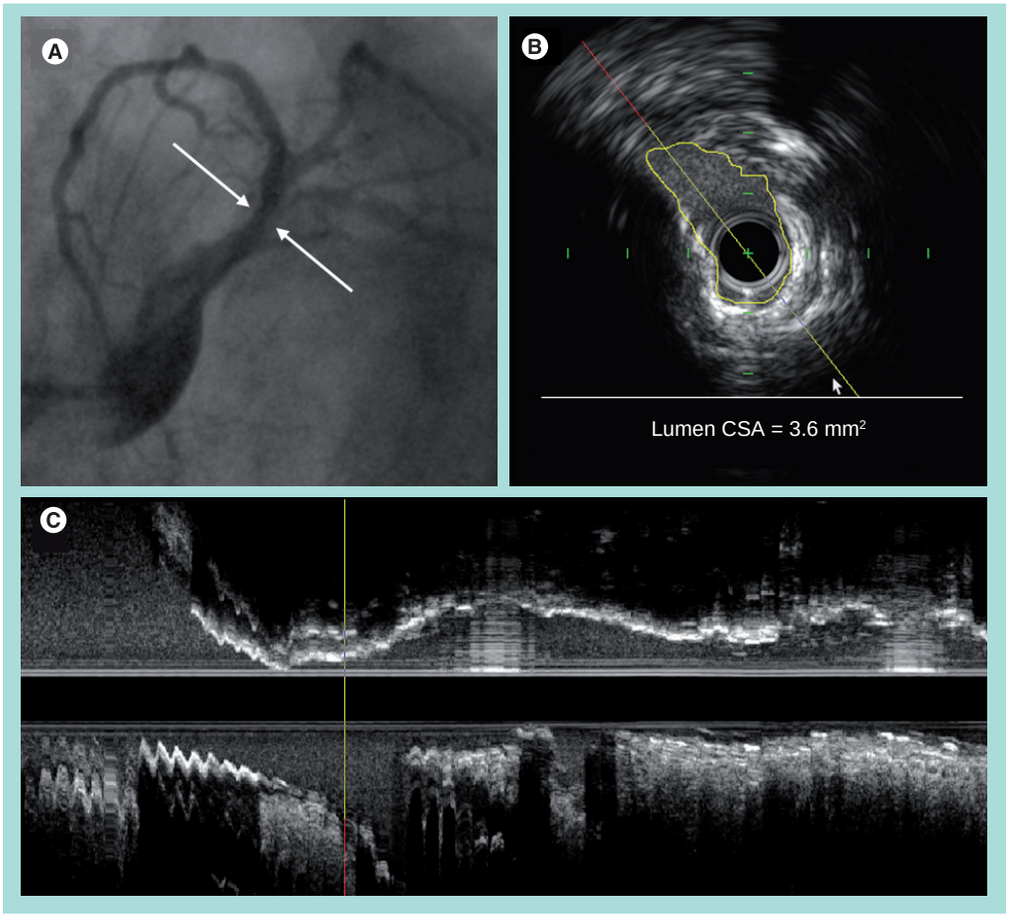

Figure 5. The value of intravascular ultrasound in left main trunk coronary disease.
(A) Coronary angiogram showing the presence of a hazy lesion involving the distal left main trunk (arrows) that determines a moderate stenosis (40%). **(B & C)** Intravascular ultrasound imaging showing the presence of a severe calcified lesion that determines a severe stenosis (minimal CSA of 3.6 mm^2).
CSA: Cross-sectional area.

of 6.0 mm^2 is used as a cutoff value for revascularization decisions, and we routinely use IVUS for decision making and for guidance of PCI of the LMCA.

■ Undilatable lesions

Severely calcified coronary lesions are frequently missed by angiography (Figure 6) [3] and their treatment using balloon angioplasty has been associated with decreased angiographic success and increased complications [49]. Stenting in these cases results in an unexpanded stent and higher rates of restenosis and thrombosis. Despite an apparently well-inflated balloon, lesions with concentric calcium remain undilatable and should not be stented until well prepared by the use of rotablator [50]. Rotablator remains the only effective tool to prepare these lesions for stenting. Rotablator modifies the compliance of the lesion and does not necessarily ablate much plaque. Furthermore, the presence of long, severely calcified coronaries might contraindicate PCI, indicating surgical revascularization when feasible.

■ Ostial lesions

IVUS can easily differentiate between true ostial lesions, where the MLA and the maximum plaque burden are located at the ostium, and 'pseudo-ostial' lesions, wherein it is possible to identify a proximal reference segment (Figure 7). We highly recommend the use of IVUS for all ostial lesions. Severe, concentric calcification is frequent in this location, especially when aorto-ostial, and these lesions should never be stented without prior effective plaque dilation.

■ Bifurcation lesions

We also use IVUS in most bifurcations, obtaining imaging of both branches. Angiographic involvement of the side branch increases the risk for side-branch occlusion [51] and MI (Figure 8) [52].

In a retrospective IVUS series of 81 bifurcated lesions undergoing PCI, Furukawa *et al*. reported that the presence of plaque involving the side branch ostium was associated with side branch occlusion in 35% of cases versus 8% when the side branch was not involved (p = 0.003); here also, angiography could not predict the extent of ostial branch involvement [53]. In view of the latest clinical trial results, provisional stenting has become the standard approach, for bifurcation lesions. In the presence of true bifurcation lesions, which is better demonstrated by ostial side branch disease on IVUS, treatment of the side branch is recommended [54]. If the side branch flow is deteriorated on the provisional stenting approach additional specific treatment of the side branch is recommended [54]. When dedicated intervention is performed in the side branch, the result must be ensured and optimized by IVUS guidance, even in the presence of optimal angiographic appearance [55,56].

■ Saphenous vein grafts

Conventional angiography underestimates the severity of vein graft remodeling and athermanous plaque development compared with IVUS [57]. Early SVG evaluation after surgery has shown that significant wall thickening occurred by 6 months, accompanied by compensatory enlargement and preservation of the graft luminal diameter [58]. Atheromatous plaque could be detected by IVUS as early as 8–10 months postgrafting in association with both expansive and constrictive remodeling [59]. Morphologically, vein graft atherosclerosis tends to be diffuse, concentric and friable, with a poorly developed or absent fibrous cap and little evidence of calcification [60]. As a result, PCI of degenerative SVG represents a clinical dilemma since it is associated with a higher risk of distal embolization, subsequent MI and late cardiac events when compared with native vessel PCI [61–63]. Consistently, several randomized clinical trials have established the use of an embolic protection device as the standard of care for SVG intervention [64]. In addition, we recently reported the clinical benefit of the 'undersized' DES approach in large veins (n = 209), which may be used as an adjunctive strategy to embolic protection devices [65]. We observed that the undersized stenting approach, defined as a stent size under 89% of the reference lumen, was associated with a reduction in frequency of postprocedural creatinine kinase-MB elevation, significantly less plaque prolapse shown

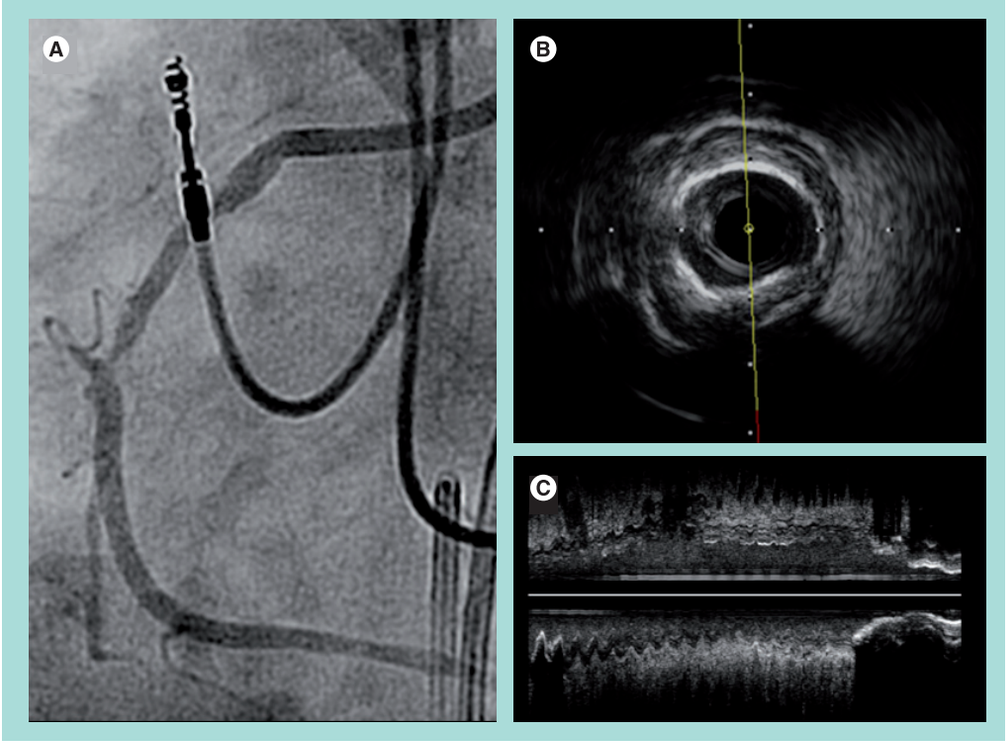

Figure 6. Undetected angiographic coronary calcification. (A) Right coronary angiogram showing the presence of a severe focal stenotic lesion in the midsegment, with unsuspected calcification. Intravascular ultrasound probe did not cross. **(B)** Intravascular ultrasound imaging at the site of the obstruction showing the presence of severe concentric calcific plaque. **(C)** Intravascular ultrasound long view of the same vessel.

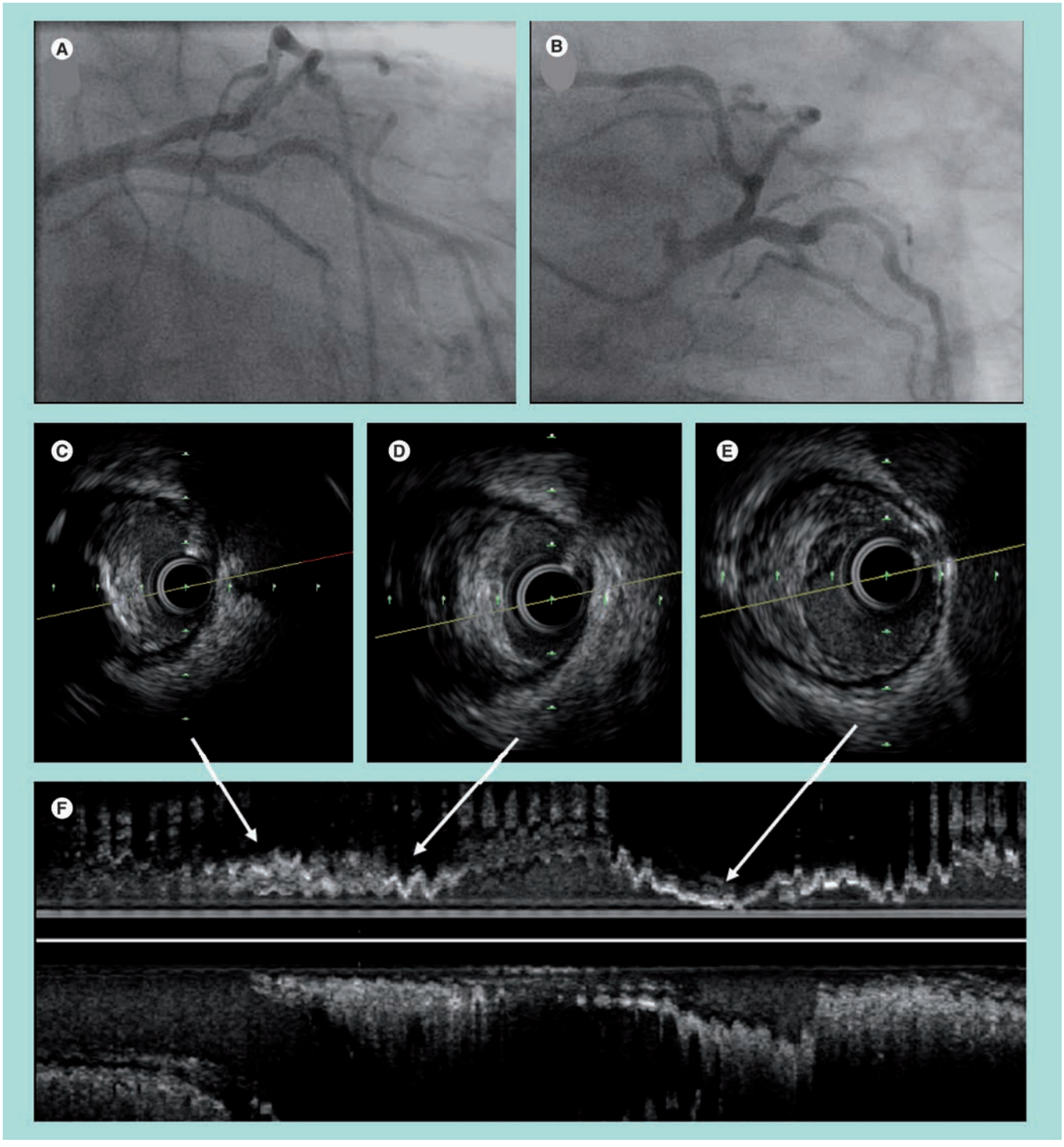

Figure 7. A 65-year-old woman presenting with progressive shortness of breath and chest pain. (A & B) Coronary angiogram showed the presence of mild disease involving the proximal left anterior descending artery segment. Intravascular ultrasound imaging of the left anterior descending artery showed the presence of an excentric, mixed plaque that determined a severe stenosis in the proximal segment (**[C & D]** show cross-sectional views, and **[F]** shows long-run view), and a more distal, soft plaque (**[E & F]** show cross-sectional and long-run views, respectively), also missed by the angiography.

by IVUS and, most importantly, no increase in the rate of 1-year TLR. As a general rule, IVUS is not used before stenting in degenerated grafts to prevent embolization. If the lesion is distal in a vein graft, IVUS can be used proximally to assess vessel size. At our institution, IVUS is always performed after stenting to assess results. Lack of apposition of these undersized stents is frequent and is not associated with any clinical adverse event [56].

■ In-stent restenosis

Intravascular ultrasound is an indispensable tool in the evaluation of patients with failed stents: ISR. We have demonstrated that 24% of patients referred for treatment of ISR did not have restenosis but instead had mechanical problems, such as underexpanded stents, stent fracture or stent malapposition [38]. If stent underexpansion is demonstrated, the stent should be properly expanded; if incomplete malapposition is shown, appropriate apposition must be achieved and confirmed by IVUS [66]. IVUS often shows segments of hyperplasia that are much longer than appreciated by angiography. Evaluation of the reference vessel by IVUS is also important before treating ISR [38,67]. When approaching a BMS failure, after excluding a mechanical problem, a DES implantation has became the standard recommended therapy [68]. In the case of DES failure, the therapeutic approach represents a major dilemma since no evidence allows the recommendation of any particular treatment. Nonetheless, we believe that IVUS guidance will help to improve therapy selection based on the possible underlying mechanism. When the ISR pattern appears focal (<10–20 mm), the more logical approach would be to perform high pressure balloon dilatation, confirming the result by using IVUS [66]. When dealing with diffuse DES restenosis (>20 mm) demonstrated by IVUS – a large amount of neointimal hyperplasia that implies an exaggerated neointimal response to stenting – a more aggressive treatment modality seems to be justified, such as repeating DES implantation [69], brachytherapy [70], drug-coated balloons [71] or surgical revascularization. The results from the recently published randomized Intracoronary Stenting and Angiography Results: Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) 2 study demonstrated that implantation of a second DES is feasible and safe to treat sirolimus-eluting stent (SES) restenosis [72]. This study demonstrated that either repeat SES or a switch to paclitaxel-eluting stents (PES) is associated with comparable efficacy [72]. Nonetheless, no study has demonstrated superiority of any strategy, and the best therapeutic approach to treat DES ISR remains unclear.

■ Differential diagnosis of coronary artery disease

Conventional angiography depicts coronary anatomy from a planar 2D silhouette of the lumen. Therefore, when using angiography only, a variety of coronary conditions are misinterpreted as 'normal' when in fact they are not [73]. In this context, IVUS use might add important prognostic information and guide the appropriate therapy, as described for the following situations described in the next sections.

Myocardial infarction with 'normal' angiography

The typical pathological process underlying MI is ruptured plaque and thrombus formation and/or lumen compromise, usually identified by angiography as complex coronary lesions [74]. Thrombus is usually recognized by IVUS as an intraluminal echolucent mass; however, IVUS diagnosis is not pathogenomic and should always be considered presumptive [5]. Nevertheless, some conditions may present clinically as MI with apparently normal coronaries on angiogram, such as spontaneous dissections, coronary spasm (especially related to the cocaine abuse) and 'silent' ruptured plaques, conditions that are better recognized and differentiated by IVUS. We have seen many examples of 'Takotsubo'-like syndrome where IVUS showed ruptured plaque in the LAD, despite an apparently normal coronary angiogram (Figure 9), suggesting that the etiology

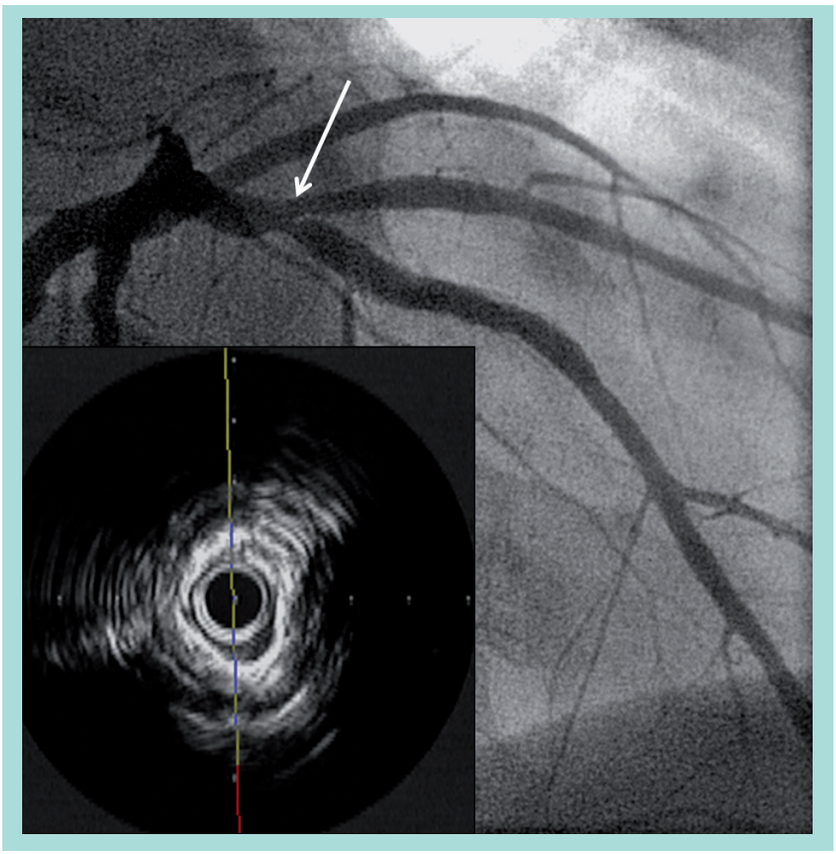

Figure 8. Angiogram of the left anterior descending artery showing the presence of a lesion right after the origin of a large diagonal branch.
Ostium of the diagonal branch is indicated by an arrow. Intravascular ultrasound imaging of the diagonal branch showed extensive compromise of the ostium with unsuspected severe concentric calcium.

may have been transient occlusion of the vessel at the site of plaque rupture with stunning of the myocardium. We also reported that the left ventricular 'ballooning' characteristic of Takotsubo syndrome may be observed in approximately 25% of patients with acute occlusion of the LAD (Figure 9) [75]. Therefore, in the absence of typical angiographic findings of an acute MI or in the absence of the typical presentation consistent with Takotsubo syndrome, we recommend IVUS evaluation. When a ruptured plaque is demonstrated, treatment with high-dose statins and antiplatelets is indicated.

Angiographic filling defects

Although most of the angiographic filling defects correspond to thrombi, a percentage of them are represented by different calcified plaque patterns [76]. In a retrospective analysis of 78 angiographic filling defects, 48 (61.5%) had IVUS evidence of thrombus and 30 did not (38.5%) [77]. A total of 13 (16.7%) were calcified plaques on IVUS not seen angiographically. In addition, of the 48 IVUS thrombus-containing lesions, nine (18.8%) showed thrombus superimposed on calcified plaque.

Angiographic haziness

Hazy angiographic lesions can represent the full spectrum of morphologies, including calcium, thrombus, dissections and large plaque burdens with positive remodeling.

Coronary spasm

Vasospastic angina may occur in the absence of angiographic lesions. However, IVUS studies have demonstrated that noncalcified plaques or diffuse intimal thickening associated with negative remodeling is frequently present at the site of vasospasm [78,79].

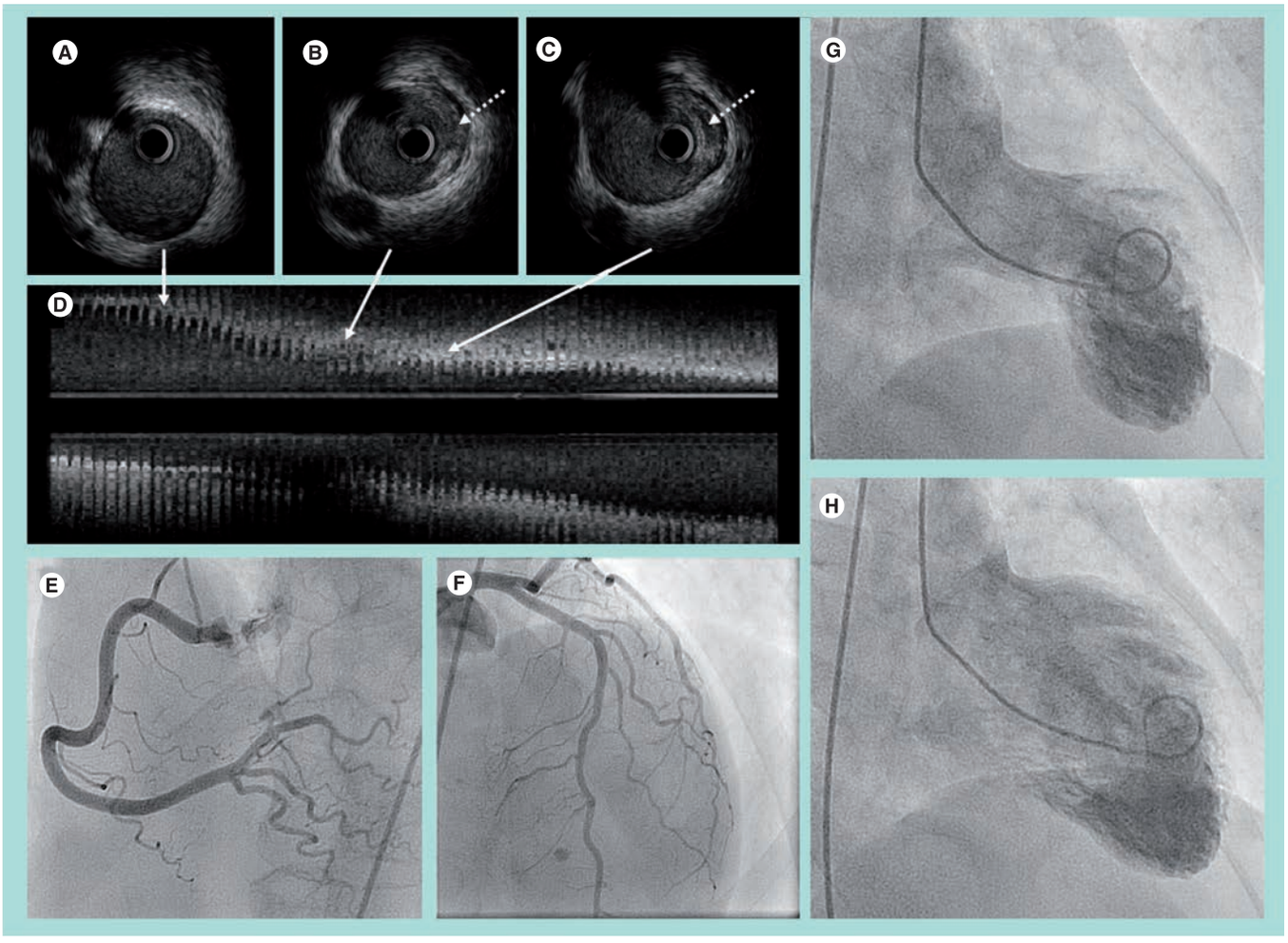

Figure 9. A 60-year-old woman presenting with severe chest pain after an emotional distress. (A–D) Intravascular ultrasound imaging showed the presence of a proximal ruptured plaque (dashed arrows) in the proximal left anterior descending artery. **(E & F)** Angiography showed normal coronaries. **(G & H)** Ventricle angiogram showed the typical abnormal contraction pattern described in 'Takotsubo cardiomyopathy'.

Therefore, we propose a more liberal use of IVUS for patients presenting with ambiguous angiographic coronary lesions and/or undergoing potentially complex interventions to improve diagnostic accuracy and appropriate guidance.

Postprocedural IVUS guidance

The role of IVUS in the optimization of stent implantation has been established when IVUS observations revealed that incomplete stent apposition significantly contributes to early ST occurrence [80]. These observations led to the widespread adoption of high-pressure balloon postdilatation after stent deployment [81]. As earlier described, the results of the AVID, TULIP, and SIPS support the routine use of IVUS to ensure good stent expansion and apposition when using BMS [6,21,22,82]. However, with the emergence of DES and significant late loss decreases, different authors suggest that routine IVUS guidance after DES deployment is not required. Nevertheless, incomplete stent expansion and smaller minimum stent area after DES implantation measured by IVUS are reported to correlate with restenosis [8,83] and ST [9,10]. In addition, using the traditional criteria for inadequate stent expansion, defined per the Multicenter Ultrasound Stenting in Coronaries (MUSIC) study (final stent CSA >80% of the reference CSA, or >90% if reference CSA area was <9 mm^2) [84], we reported significantly higher rates of stent underexpansion with SES and PES at conventional delivery pressures [85,86]. In view of the exposed evidence, we support a more liberal use of IVUS to ensure an appropriate result after stent deployment, especially when concerned with approaching complex coronary lesions or patients who are theoretically at higher risk of ST.

Postintervention complications

The rate of persistent angiographic haziness proximal or distal to the stent is approximately 15% after high-pressure stent deployment. Stent edge dissection is the most common reason;

Executive summary

Utility of intravascular ultrasound in intermediate coronary lesions

- Cutoff values for minimal lumen area under 4.0 mm^2 and percentage area of stenosis over 60–70% correlate appropriately with fractional flow reserve value under 0.75 and clinical outcomes in large none left main vessel (>3.0 mm reference diameter).
- Intravascular ultrasound (IVUS) and fractional flow reserve should be used as complementary tools.

Clinical evidence for routine use of IVUS guiding percutaneous coronary intervention

- The results of the Angiography Versus Intravascular Ultrasound-Direct Stent Placement (AVID), the Thrombocyte Activity Evaluation and Effects of Ultrasound Guidance in Long Intracoronary Stent Placement (TULIP) and the Strategy for Intracoronary Ultrasound-Guided PTCA and Stenting (SIPS) randomized trials support the routine use of IVUS to ensure good stent expansion and apposition when using bare-metal stents.
- Incomplete stent expansion and smaller minimum stent area after drug-eluting stent implantation correlate with restenosis and stent thrombosis.
- Retrospective data suggest that routine intravascular ultrasound-guided percutaneous coronary intervention using drug-eluting stent might decrease the risk of acute stent thrombosis and improve the outcomes in unprotected left main trunk percutaneous coronary intervention.

Role of IVUS sizing & choosing the interventional device

- A precisely sized device and interventional strategy based on IVUS findings is recommended.

Role of IVUS in complex coronary interventions

- Routine IVUS guidance is recommended for complex coronary intervention including:
  - Protected and unprotected left main trunk disease
  - Undilatable lesions
  - Ostial lesions
  - Bifurcations
  - Saphenous vein graft
  - In-stent restenosis

IVUS value in the differential diagnosis of coronary artery disease

- IVUS use might add important prognostic information and guide the appropriate therapy in the following situations:
  - Myocardial infarction with 'normal' angiography
  - Angiographic filling defects
  - Angiographic haziness
  - Coronary spasm

IVUS assessment of complications after percutaneous coronary intervention

- Stent edge dissection is frequent as detected by IVUS, usually a benign phenomenon that does not require additional stent implantation if the area stenosis is less than 60% at the site of dissection.

however, other conditions, such as thrombus, calcification, intramural hematoma or material prolapse could be distinguished by IVUS and further treated if necessary. Stent edge dissection is a frequent phenomenon detected by IVUS and does not necessarily proscribe an adverse prognosis [87]. Indeed, Nishida *et al*. reported the results of 124 consecutive native coronary lesions with angiographic non-obstructive residual dissection in 97 patients compared with 124 lesions in 100 matched patients without residual dissection [88]. They observed that most nonflow-limiting residual dissections occurring after successful PCI have a good long-term prognosis and do not need additional stenting. More importantly, IVUS examination identifies an area stenosis over 60% at the site of dissection to be the best threshold for distinguishing patients who had in-hospital major adverse cardiac events. Therefore, we encourage IVUS guidance for complications occurring after PCI, especially to prevent the unnecessary deployment of additional stents.

Conclusion

As a result of the described evidence and our clinical experience, we provided a comprehensive approach for a practical use of IVUS in a modern catheterization laboratory. We believe that routine use of IVUS, especially when approaching complex coronary lesions, allows for better definition of the nature of the disease, thereby leading to a more tailored and focused therapeutic strategy resulting in an optimal interventional outcome. As multiple new therapies become available, where efficacy is the main objective, but safety is the major concern, we support a more liberal use of IVUS.

Future perspective

IVUS imaging has played a key role in the understanding and development of currently available coronary intervention technologies. Multiple datasets support the concept that routine use of IVUS impacts positively procedural results and long-term outcomes. Nonetheless, few data are available on how the preprocedural use of IVUS might impact intervention strategy and clinical outcome, and limited studies have specifically addressed this issue in the DES era. As percutaneous intervention is expanding into more complex and high-risk lesion subsets, and higher-risk patients, IVUS guidance may become more important for improved short- and long-term outcome; prospective, randomized clinical designs would be ideal to prove this concept.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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