Incomplete stent apposition (ISA) is characterized by the lack of contact of at least 1 stent strut with the vessel wall in a segment not overlying a side branch; it is more commonly found in drug-eluting stents than bare-metal stents. The accurate diagnosis of ISA, initially only possible with intravascular ultrasound, can currently be performed with higher accuracy by optical coherence tomography, which also enables strut-level assessment due to its higher axial resolution. Different circumstances related both to the index procedure and to vascular healing might influence ISA occurrence. Although several histopathology and clinical studies linked ISA to stent thrombosis, potential selection bias precluded definitive conclusions. Initial studies usually performed single time point assessments comparing overall ISA percentage and magnitude in different groups (i.e., stent type), thus hampering a comprehensive understanding of its relationship with vascular healing. Serial intravascular imaging studies that evaluated vascular response heterogeneity recently helped fill this gap. Some particular clinical scenarios such as acute coronary syndromes, bifurcations, tapered vessels, overlapping stents, and chronic total occlusions might predispose to ISA. Interventional cardiologists should be committed to optimal stent choices and techniques of implantation and use intravascular imaging guidance when appropriate to aim at minimizing acute ISA. In addition, the active search for new stent platforms that could accommodate vessel remodeling over time (i.e., self-expandable stents) and for new polymers and/or eluting drugs that could induce less inflammation (hence, less positive remodeling) could ultimately reduce the occurrence of ISA and its potentially harmful consequences.

Incomplete Stent Apposition and Potential Relationship With Adverse Clinical Outcomes

A clear relationship between ISA and adverse cardiovascular events is still controversial. Although some studies have acquired (i.e., not present post-procedure, but identified at follow-up assessment). In the absence of baseline intravascular imaging assessment, it is described simply as late ISA (2,3). Several factors are responsible for this pathological phenomenon and its different presentations, as follows: 1) inadequate stent implantation—in this setting, there are basically 2 possibilities: a) marked mismatch between stent size selection and luminal dimensions (i.e., stent diameter smaller than reference lumen diameter), a situation in which, regardless of optimal stent expansion, ISA will occur (4); or b) stent underexpansion despite an adequate stent–artery ratio due to several different factors, such as inadequate pressure of implantation and/or plaque-related factors (Fig 1); 2) chronic stent recoil (5); 3) thrombus dissolution after primary percutaneous coronary intervention (PCI) (6); 4) positive vessel remodeling (6–11); and 5) inadequate (i.e., insufficient and/or delayed) neointimal hyperplasia (12–15).
failed to demonstrate such connections (7,16–18), others have done so (12,19–24) (Table 1). Lee et al. (25) demonstrated that among 30 patients with very late stent thrombosis (ST), 73.9% of the drug-eluting stent (DES) group exhibited ISA (among whom 64.7% had late acquired ISA), whereas none of the bare-metal stent (BMS) group had ISA. Although the results showed a higher incidence of ISA in patients with DESs compared with BMSs, confirming data from previous reports (20), they also highlighted that ISA is not an isolated factor responsible for DES thrombosis (i.e., 26.1% of DES patients had stent thrombosis without evident ISA) (25). Guagliumi et al. (26) demonstrated by combined IVUS and OCT assessments that the presence and magnitude (i.e., area and distance) of ISA were significantly higher in patients with DES thrombosis compared with those without DES thrombosis. In addition, these investigators implicated 1 mechanism that led to ISA (i.e., positive remodeling) and another mechanism that could be a consequence of ISA (i.e., uncovered stent struts) as independent predictors of DES thrombosis (Fig. 2). Eosinophilic-rich inflammatory infiltrates associated with positive remodeling were also demonstrated (27). Alfonso et al. (27) also identified ISA in patients with ST using IVUS and OCT (ISA was identified in 40% and 47% of patients, respectively). Kang et al. (28) performed OCT imaging in 33 patients with very late ST and found that in the DES group, 52% and 64% had ISA and thrombi, respectively, whereas no patients presented with ISA in the BMS group. ISA was also more frequently found in 124 patients with very late definite DES versus BMS thrombosis (52% vs. 16%, respectively, p = 0.005) in a multicenter registry. Notably, greater ISA area was also demonstrated in the DES group compared with the BMS group. Moreover, among the DES group, a higher prevalence of ISA was identified in sirolimus-eluting stents (SES) compared with paclitaxel-eluting stents (PES) (58% vs. 37%, respectively, p = 0.02) (29). More recently, higher rates of ISA were revealed in 34 patients with DES (56%) and BMS (11%) thrombosis in Italy (30). Although extremely insightful, cautious interpretation of these results is crucial due to potential selection bias.

Understanding the underlying mechanisms involved in ISA is of paramount importance to the interventional cardiologist because it enables the identification of which features are potentially modifiable and which resources should be utilized during the index intervention to optimize implantation quality and minimize the likelihood of having ISA and its potentially harmful consequences (31–33). Although physiological vascular healing after stent implantation leads to progressive reduction of ISA over time (12–14,34,35), recent serial OCT assessments elucidated this complex mechanism more clearly, showing that the greater the acute ISA (i.e., after the index procedure), the higher the possibility of its persistence at follow-up (14,15). Furthermore, these studies demonstrated that acute ISA affects the overall vascular response negatively, ultimately leading to delayed stent strut coverage (12–15) and even to ST (12). The comprehension of this complex scenario, moreover, is key for investigators and biomedical engineers so that they can actively search for constant improvements in mechanical (i.e., stent platforms) (36) and biological (i.e., antirestenotic drugs, polymers) (37) components of coronary artery scaffolds.

**Histopathology Investigations**

Histopathology studies have been instrumental in enabling a better understanding of mechanisms that lead to ISA. The pivotal demonstration by Virmani et al. (37) that Cypher (Cordis, Johnson & Johnson, New Brunswick, New Jersey) SES thrombosis was linked to hypersensitivity reactions and to a complex proinflammatory milieu raised the initial concerns regarding the safety issues of DESs (37). The investigators identified the presence of ISA with thick layers of fibrin thrombus separating stent struts from the vessel wall. In a larger series of patients, Joner et al. (38) ratified the complexity of the multifactorial scenario (i.e., procedural and clinical related features) associated with DES failure, describing the presence of ISA coupled with delayed arterial
Table 1  Impact of ISA on Cardiovascular Events

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Design</th>
<th>N</th>
<th>Clinical Presentation</th>
<th>Type of Stent</th>
<th>Assessed by</th>
<th>Follow-Up (Months)</th>
<th>Assessment of Malapposition</th>
<th>Positive Association Between ISA and Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guagliumi et al. (22)</td>
<td>PP, SC</td>
<td>21</td>
<td>Stable/ACS</td>
<td>ZES</td>
<td>OCT</td>
<td>6</td>
<td>Malapposed struts per stent: 2.0 ± 4.2% (OLP), 3.8 ± 7.1% (non-OLP)</td>
<td>No</td>
</tr>
<tr>
<td>Kubo et al. (23)</td>
<td>PP, SC</td>
<td>45</td>
<td>Stable/ACS</td>
<td>SES</td>
<td>OCT</td>
<td>9</td>
<td>Malapposed struts per stent: 0.2 ± 1.2% (stable), 4.0 ± 6.7% (ACS)</td>
<td>No</td>
</tr>
<tr>
<td>Guagliumi et al. (24)</td>
<td>PP, SC</td>
<td>77</td>
<td>Stable/ACS</td>
<td>SES/PES/ZES/BMS</td>
<td>OCT</td>
<td>6</td>
<td>Malapposed struts per stent: 2.9 ± 7.0% (SES; OLP), 1.9 ± 4.2% (SES; non-OLP), malapposed struts per stent: 5.5 ± 15.6% (PES; OLP), 0.7 ± 2.1% (PES; non-OLP), malapposed struts per stent: 0.1 ± 0.2% (ZES; OLP), 0.1 ± 0.1% (ZES; non-OLP), malapposed struts per stent: 0.1 ± 0.1% (BMS; OLP), 0.2 ± 0.9% (BMS; non-OLP)</td>
<td>No</td>
</tr>
<tr>
<td>Guagliumi et al. (22)</td>
<td>PP, SC</td>
<td>42</td>
<td>Stable/ACS</td>
<td>EES CoCr/EES PtCr</td>
<td>OCT</td>
<td>6</td>
<td>Malapposed struts per stent: 0.5%, malapposition area 0.02 mm² (EES CoCr), malapposed struts per stent: 0.0%, malapposition area 0.01 mm² (EES CoCr)</td>
<td>No</td>
</tr>
<tr>
<td>Hong et al. (16)</td>
<td>RP, SC</td>
<td>557</td>
<td>Stable/ACS</td>
<td>SES/PES</td>
<td>IVUS</td>
<td>6</td>
<td>LSM CSA: 3.0 ± 1.9 mm² (SES), 3.2 ± 1.9 mm² (PES) (LSM occurred in 12.1% of lesions)</td>
<td>No</td>
</tr>
<tr>
<td>Steinberg et al. (17)</td>
<td>PP, MC</td>
<td>1,580</td>
<td>Stable/ACS</td>
<td>PES/BMS</td>
<td>IVUS</td>
<td>9</td>
<td>Late-acquired ISA was identified in 2.7% of BMS, 3.1% of PES-SR, and 15.4% of PES-MR</td>
<td>No</td>
</tr>
<tr>
<td>Tanabe et al. (18)</td>
<td>PP, MC</td>
<td>469</td>
<td>Stable/ACS</td>
<td>PES/BMS</td>
<td>IVUS</td>
<td>6</td>
<td>Mean ISA area: 3.6 ± 1.2 mm² (PES-SR), 2.1 ± 1.4 mm² (PES-MR), 3.0 ± 2.1 mm² (BMS)</td>
<td>No</td>
</tr>
<tr>
<td>Cook et al. (19)</td>
<td>PP, MC</td>
<td>194</td>
<td>Stable/ACS</td>
<td>SES/PES</td>
<td>IVUS</td>
<td>8</td>
<td>Max ISA CSA: 4.5 ± 5.0 mm² (SES), 5.0 ± 5.1 mm² (PES), total ISA length: 2.3 ± 1.4 mm (SES), 1.0 ± 0.9 mm (PES)</td>
<td>Yes (the presence of ISA after DES implantation was associated with a higher rate of MI and VLST)</td>
</tr>
<tr>
<td>Cook et al. (21)</td>
<td>PP, SC</td>
<td>188</td>
<td>Stable/ACS</td>
<td>SES/PES</td>
<td>IVUS</td>
<td>8</td>
<td>Max ISA CSA: 8.3 ± 7.5 mm² (VLST), 4.0 ± 3.8 mm² (control), max ISA length: 6.3 ± 6.3 mm² (VLST), 1.5 ± 1.0 mm² (control)</td>
<td>Yes (ISA is highly prevalent in patients with VLST after DES implantation)</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome(s); BMS = bare-metal stent(s); CoCr = cobalt-chromium; CSA = cross-sectional area; EES = everolimus-eluting stent(s); ISA = incomplete stent apposition; IVUS = intravascular ultrasound; LSM = late stent malapposition; MACE = major adverse cardiac event(s); MC = multicenter; MI = myocardial infarction; MR = moderate-release; OCT = optical coherence tomography; OLP = overlapping; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; PP = prospective; PtCr = platinum-chromium; RP = retrospective; SC = single center; SES = sirolimus-eluting stent(s); SR = slow-release; VLST = very late stent thrombosis; ZES = zotarolimus-eluting stent(s).
healing and the presence of fibrin surrounding the stent struts as 1 of the mechanisms associated with ST (35) (Fig. 2). More recently, Cook et al. (39) correlated the histopathology of thrombus aspirates with IVUS findings in patients with very late DES thrombosis. Interestingly, they were able to establish a correlation between the amount of eosinophil infiltrates with the extent of positive vessel remodeling, suggesting hypersensitivity reactions of all 3 layers of the vessel wall in patients with ISA; in patients without positive remodeling, however, only a few or no eosinophils were detected. Despite the outstanding contribution of histopathology research toward a better comprehension of the mechanisms that lead to ISA and its potential consequences, the data presented by these studies should be carefully interpreted because they represent a highly selected population (i.e., patients who had a DES implanted and died). Therefore, although ISA is suggested as 1 of the potential mechanisms linked with adverse cardiovascular events in these studies, a linear cause and effect relationship cannot be derived from these findings.

Another significant role played by histopathology in this scenario is the validation of intravascular imaging findings, which is of utmost importance because they enable accurate in vivo qualitative (rather than merely quantitative) assessments of vascular responses in a prospective fashion, which could ultimately facilitate the understanding of the pathophysiology of ISA. The feasibility and accuracy of tissue characterization utilizing OCT has been previously demonstrated (40–42). This could be particularly important to help elucidate, for example, the underlying mechanisms that lead to ISA in different scaffolds (Fig. 3) (43). Radu et al. (44) suggested the term “pseudoapposed” to define stent struts that were “apposed” to low-signal intensity regions, which were likely composed of acellular material such as fibrin or proteoglycan.
proteoglycan, and similar to what has been described by histopathology (38). Further investigations are required to assess the relevance of these findings.

**Fundamental Differences Between IVUS and OCT in ISA Interpretation**

Due to their high resolution, intravascular imaging modalities are essential to properly diagnose ISA in vivo. Although a complete description of IVUS and OCT imaging is beyond the scope of this paper, it is important to be cognizant of the fundamental differences and potential additive values of these imaging systems in the diagnosis of ISA, hence, facilitating data interpretation.

IVUS is a sound-based imaging system with an axial resolution of approximately 150 μm and a penetration of 4 to 8 mm. It enables detailed assessment of vessel size because the external elastic membrane is clearly visualized, therefore allowing accurate quantification of positive vascular remodeling (45,46). The diagnosis of ISA by IVUS is determined by the presence of blood speckle (or also by color Doppler imaging in the case of lower frequency IVUS) behind the stent struts not overlying a side branch. Data are provided in cross-sectional (i.e., area of ISA) and longitudinal (i.e., volume of ISA) levels (6). Conversely, OCT is a near-infrared, light-based system with an approximately 10-fold higher resolution (approximately 10–15-μm axial resolution) compared with IVUS, but with less tissue penetration (1 to 3 mm). This lack of deep tissue penetration precludes accurate quantification of positive vessel remodeling, whereas the blood-free environment obtained during OCT image acquisition, coupled with its higher axial resolution, provides a sharper delineation of the stent–lumen interface compared with IVUS, thus allowing easier image interpretation (1,47) (Fig. 4). Several authors demonstrated that OCT is superior to IVUS in detecting ISA, including in the left main coronary artery (1,12,27,48). Another important piece of information added by OCT on top of cross-sectional and longitudinal levels of assessment is the strut–lumen level analysis, which enables the diagnosis and quantification of ISA in each individual strut. It is also important to highlight that the initial diagnosis of ISA by OCT, including that performed in the catheterization laboratory in our daily practice, is qualitative, whereas the final determination of whether or not 1 strut exhibits ISA is quantitative (i.e., considering blooming, strut, and polymer thicknesses) (Fig. 5) (49,50). Taken together, these characteristics indicate that IVUS and OCT complement each other in the diagnosis and elucidation of ISA mechanisms (26,27).

**Study Designs and Endpoints**

Several studies have evaluated ISA by single time point (i.e., follow-up) assessments (51–55). Although the information provided by these studies is extremely valuable in the determination of ISA rates using different stents in vivo, it is impossible to completely elucidate this morphological feature in a single “snapshot.” Healing after stent implantation is a continuum influenced by several different factors, related to both baseline characteristics (i.e., clinical and procedure related) and to alterations that occur along this complex biological process (i.e., inflammation, delayed healing, and positive remodeling); therefore, serial intravascular imaging studies using IVUS and/or OCT (11,12,14,15,35,56) have helped to fill the gap left by single time point assessments. Despite the importance of serial invasive imaging assessments to comprehensively characterize the natural history of ISA, increased costs, coupled with ethical issues of submitting patients to the inherent risks of repeated invasive interventions, x-ray exposure, and contrast media injections, have hampered their more extensive utilization (57,58).

Another consideration is that data presentation across studies evaluating ISA lacks standardization. The majority of trials provide overall percentages, areas, and volumes of ISA associated with the groups (i.e., different stents) being evaluated (59,60), rather than identifying and quantifying segments in which the abnormality is present (i.e., lesion-level assessment) (61), therefore restricting the assessment of intra- and interindividual heterogeneity of vascular responses, and consequently, of ISA. Räber et al. (62) demonstrated that, despite an overall equivalent percentage of ISA late after SES and PES implantation, significant clustering of ISA was depicted in the former, suggesting different patterns of vascular responses between the scaffolds being evaluated. Gutiérrez-Chico et al. (15) described heterogeneous morphological healing patterns in patients with acute ISA using serial OCT imaging assessments. Another tool to assess whether heterogeneity exists in vascular responses is the coefficient of variation, which is obtained by dividing each lesion into subsegments (i.e., dividing the standard deviation by the mean percentage of ISA) (35,63–65). These analytical approaches could ultimately expand our knowledge of assessing pathological vascular reactions to stents, particularly ISA, and avoiding, for instance, the “diluting” of the results of clustered ISAs that may occur in localized segments of certain individuals, and in the entire population of the study. Whether these findings significantly affect clinical outcomes remains to be demonstrated.

**Incomplete Stent Apposition in Different Clinical Scenarios**

**Acute coronary syndromes.** Nakazawa et al. (66) used histopathology to demonstrate that vascular healing was delayed and ST rates were increased in patients who underwent DES implantation for myocardial infarction compared with stable angina; culprit sites in the former had greater fibrin deposition and inflammation, together with less neointimal proliferation. In addition, higher rates of struts penetrating the necrotic core and greater external elastic membrane areas were found. Hong et al. (67) showed in vivo
that BMS implantation during primary PCI was an independent predictor of late ISA, but it was not linked to increased rates of adverse events at 3-year follow-up. In a serial assessment by IVUS, BMS and PES rates of acute ISA were equivalent, whereas PES were more frequently associated with late acquired ISA, mostly because of thrombus dissolution and positive remodeling. The investigators also found that an area of acute ISA >1.2 mm² determined resolved ISA from persistent ISA (6). Likewise, no differences were observed between SESs and BMSs regarding acute ISA rates after primary PCI (38.5% and 33.8%, p = 0.51), whereas late acquired ISA was more often identified in SES, mainly secondary to positive vessel remodeling (84% of the cases) (68). Data obtained from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study did not link early stent thrombosis with the presence of acute ISA (69); in addition, the 13-month follow-up of the HORIZONS-OCT study included 188 stents (PES and BMS) and showed higher rates of late ISA with PES.
compared with BMS (70). Gonzalo et al. (71) used OCT imaging to demonstrate, in vivo, that DESs implanted during primary PCI compared with stable and/or unstable angina more often had ISA at 9-month follow-up (75% vs. 25.8%, respectively, \( p = 0.001 \)). The investigators also identified DES implantation during primary PCI as the only independent predictor of ISA (odds ratio: 9.8, 95% confidence interval: 2.4 to 40.4; \( p = 0.002 \)). Davlouros et al. (72) showed in a small study that ISA was correlated with a lack of coverage 6 months after PES implantation for acute coronary syndromes. Kubo et al. (23) compared unstable versus stable angina patients who underwent DES implantation and demonstrated significantly higher rates of both acute (67% vs. 32%; \( p = 0.038 \)) and late ISA (33% vs. 4%, respectively; \( p = 0.012 \)) in the former setting; no adverse events were reported in the 55 patients in this study at 9-month follow-up. Adrenergic vasoconstriction, which leads to underestimation of the reference vessel size, which then leads to an equivocal stent choice (i.e., smaller than vessel dimensions), is another potential cause of ISA after acute myocardial infarction (73). The European Guidelines on ST-segment elevation myocardial infarction recommend intracoronary administration of nitrates for more accurate stent sizing during primary PCI (74).

**Figure 4** ISA by IVUS and OCT

In A-I, an intravascular ultrasound (IVUS) cross-sectional image shows stent struts (red arrows) with ISA (yellow asterisks). The same co-registered region of interest is demonstrated in an OCT image (A-II), in which one can also identify the stent struts (red arrows) with ISA (yellow asterisks). In B-I, however, the IVUS image does not enable a clear diagnosis of ISA, whereas in the same co-registered region (B-II) imaged by OCT, the presence of stent struts (red arrow) with ISA (yellow asterisks) is clearly depicted. The blue lines in the longitudinal views located in the bottom of each cross section demonstrate the region of the pullback from which the cross sections were obtained. Abbreviations as in Figures 2 and 3.

**Figure 5** Quantification of ISA by OCT

In daily clinical practice, the initial assessment of ISA by OCT is qualitative, as demonstrated in A; however, the accurate determination of ISA is ultimately quantitative, because several factors such as polymer and strut thicknesses (different for each stent) and one-half of the blooming should be taken into account for the determination of the final malapposed distance. ISA quantification of some struts are demonstrated by the purple squares in B, whereas the region highlighted by the white square in C demonstrates a strut (blue arrow), which although seemed to be ISA by qualitative assessment, was actually properly apposed (i.e., in contact with the lumen boundary, blue dashed line), whereas another strut was demonstrated to be malapposed (green square, malapposed distance calculation on the right side of the figure). Abbreviations as in Figure 2.
Overlapping stents. In overlapping (OLP) stent regions, a greater amount of metal and increased concentrations of eluting drugs or polymers might increase the risk of flow disruption, inflammation, fibrin deposition, and thrombotic events. Finn et al. (75) performed histopathological evaluation of OLP stents in animal models and showed that although both first-generation SES and PES promoted delayed arterial healing and inflammation at OLP sites compared with BMS, PES had greater fibrin deposition and medial cell loss, as well as a greater external elastic membrane area compared with both SES and BMS. In concordance, immature neointima was found by Shinke et al. (76) in OLP PES regions; furthermore, these investigators used angioscopy to identify more thrombus in PES compared with BMS OLP regions. Recently, an in vitro assessment linked BMS deployed in ISA or OLP fashions with higher thrombogenicity compared with well-apposed, length-matched controls (1.58-fold, p < 0.001; and 2.32-fold, p < 0.001). The investigators also demonstrated that thin struts were less prone to thrombosis compared with thick-strut stents (77). The concerns raised by histopathology and in vitro data were amplified in vivo OCT evaluation performed by Tanigawa et al. (78), who demonstrated that despite the vessel size increase after OLP PCI, no significant ISA was demonstrated in the everolimus-eluting stent (EES) group in the same retrospective IVUS study at 9-month follow-up. Meanwhile, Otake et al. (80) demonstrated that despite the vessel size increase after OLP PES, no significant ISA was demonstrated; likewise, no significant ISA was demonstrated in the everolimus-eluting stent (EES) group in the same retrospective IVUS study at 9-month follow-up. In addition, Dawkins et al. (81) did not show increased ISA in OLP segments of PES. An interesting insight in this setting was recently demonstrated by Guagliumi et al. (22); similar stent platforms and antirestenotic drugs (i.e., zotarolimus), but different polymers and release kinetics, led to different rates of ISA in OLP regions (i.e., slow-release ZES showed higher rates of ISA compared with fast-release ZES). Different stent platforms (i.e., cobalt-chromium vs. platinum-chromium), but same drug-release kinetics, in EES did not reveal differences in terms of ISA (82). The importance of the underlying plaque in the results of OLP stenting was investigated by Tahara et al. (83), who demonstrated that increased rates of ISA and uncovered struts were present when OLP stenting was performed in normal-appearing arterial segments, whereas restenosis occurred exclusively in segments with previous high-grade stenosis.

Chronic total occlusions. Several different mechanisms might be implicated in ISA after chronic total occlusion PCI. Stent–vessel mismatch, which occurs because the occluded artery can appear smaller than its actual size due to chronic hyperperfusion, could be responsible for acute ISA, whereas injury to the adventitial layer caused by the guidewire, creation of a false lumen, or subintimal stenting could contribute to late acquired or persistent ISA. Hong et al. (16) identified chronic total occlusion PCI as an independent predictor of DES ISA. In the same study, the incidence of ISA in this scenario was 27.5%.

Bifurcations. Coronary artery bifurcations are complex structures in which stent–vessel interactions are dependent on several variables, such as stent strut location (i.e., flow divider or lateral wall) (84), side branch angulation, plaque distribution, or the technique used for stent implantation (i.e., 1 or 2 stents) or post-dilation (i.e., kissing-balloon or separate main vessel and side branch dilations). The difficulty of achieving adequate stent apposition utilizing 2 stent techniques in coronary artery bifurcations was demonstrated in vitro by Murasato et al. (85) and Ormiston et al. (86), and their results were consistent in an in vivo IVUS study that revealed that more than 60% of the ISA was proximal to the carina in lesions treated with the “crush” technique (87). In line with these results, Foin et al. (88) showed, in vitro, that “crush” stenting led to higher rates of ISA compared with the Culotte and T with protrusion technique. Tyczynski et al. (89) used OCT imaging to demonstrate higher rates of ISA in a side branch compared with non-side branch segments after bifurcation stenting. Interestingly, no differences between simple and complex techniques were revealed (89).

Several interventions have been proposed aimed at optimizing stent implantation in bifurcations. Distal cell guidewire re-crossing to the side branch led to a reduction of ISA both in vitro and in vivo (90,91). In the latter, OCT-oriented guidewire re-crossing to the side branch significantly reduced rates of ISA compared with angiography-oriented procedures (9.5% vs. 42.3%, respectively; p < 0.0001). Foin et al. (92) compared the use of a final kissing balloon in vitro with a 2-step (main branch and side branch) final balloon dilation technique in bifurcations. Although the investigators demonstrated equivalent rates of ISA in the side branch ostium region for both techniques, they depicted higher rates of ISA at the proximal stent edge with the kissing balloon (30.7 ± 26.4% vs. 2.8 ± 9.6% for 2 step, p = 0.0016) (92), which could be reduced by performing an additional balloon dilation in the proximal stent segment (33.4% vs. 0.6%, respectively, for nonproximal post-dilation and proximal post-dilation; p = 0.02) (93). More recently, Rahman et al. (94) demonstrated that although kissing-balloon inflations led to some amount of proximal main branch stent asymmetry, the improved stent expansion secondary to that maneuver was sufficient to adequately appose stent struts in the majority of cases. Di Mario et al. (95) proposed that stent optimization in bifurcations could be maximized by high-resolution intravascular imaging guidance. A large area of ISA, which was not suspected after angiography-guided stent optimization with a kissing balloon, was seen by
3-dimensional OCT imaging in a case of left main coronary artery distal bifurcation intervention recently described by Fujino et al (96). Among 403 patients with IVUS-guided SES implantation in the left main coronary artery (including distal bifurcation), 28 presented with acute ISA; however, no correlations between this pathological phenomenon and adverse cardiovascular events at 2-year clinical follow-up were established (97). So far, however, no clinical benefits have been found with the use of routine intravascular imaging guidance during bifurcation stenting; therefore, further research in this field is mandatory (98).

**Vessel tapering.** Vessel tapering is frequently observed in long coronary lesions, which might lead to ISA due to marked differences in vessel geometry in the same region of interest. Although multiple post-dilations with different balloon sizes is the usual strategy used with the aim of obtaining adequate apposition when stenting distinct vessel dimensions, aggressive post-dilation with balloons disproportionately larger than the nominal stent diameter can lead to stent strut deformation (99) and eventual polymer damage (100,101). This could negatively affect vascular responses. Carrozza et al. (102) described increased stent recoil with larger acute expansion diameters in which excessive DES overstretches left important gaps between the strut cells, which could induce suboptimal antirestenotic drug delivery (103). Importantly, Russo et al. (104) used an animal to demonstrate that vessel overexpansion might be counterproductive because it leads to more intense neointimal proliferation. Therefore, reaching equipoise between adequate (but not excessive) stent expansion and absence of ISA while avoiding vessel injury is a difficult goal to accomplish in tapered coronary arteries.

### Potential Alternatives to Reduce ISA in Daily Clinical Practice

As previously described, ISA is multifactorial; features directly related to the index intervention and others associated with vascular response to stents are implicated in its pathophysiology. Therefore, it is likely that combined, rather than isolated approaches, are necessary to successfully reduce ISA rates. Although a clear relationship between ISA and adverse cardiovascular events is still controversial, interventional cardiologists must be committed to minimizing acute ISA by optimizing stent choice and techniques of implantation. Some novel devices could be helpful in addition to conventional strategies in this setting. Verheye et al. (105) demonstrated promising results with the use of self-expandable nitinol stents (STENTYS, STENTYS SA, Paris, France) in coronary bifurcations. Interestingly, these devices (either BMS or PES) have small interconnections that enable easy provisional stenting and access to the side branch. Progressive stent expansion was demonstrated by increasing stent area over time, which could potentially reduce rates of persistent and late acquired ISA because the stent conforms to vascular remodeling. Minimal ISA was revealed at 6-month IVUS follow-up. This same device was tested during primary PCI and demonstrated an early reduction of ISA compared with balloon-expandable stents (106). Self-expandable stents could also help reduce ISA in tapered lesions because the same stent could properly

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**Figure 6 STEMI in a Tapered Vessel Treated With Self-Expandable Stents**

(A) An ostial occlusion in the left anterior descending artery (LAD) during ST-segment myocardial infarction (STEMI). After flow restoration (B), marked vessel tapering is observed in the mid LAD (white arrows). Final result after implantation of 2 STENTYS nitinol self-expandable stents in the mid and proximal LAD in overlapping fashion is shown in (C). White arrows identified by letters have their OCT assessments represented with the corresponding letters in E and F; a marked discrepancy in stent areas is shown, whereas distal and proximal references are shown in D and G.
accommodate different vessel dimensions along the lesion (Fig. 6), thereby avoiding complications (e.g., dissections and vessel perforation) in smaller segments while allowing optimal stent apposition in larger segments. Further investigations are necessary to establish whether self-expandable stents could reduce adverse clinical outcomes compared with balloon-expandable stents in all of these clinical settings.

More recently, everolimus-eluting bioresorbable vascular scaffolds (Absorb, Abbott Vascular, Santa Clara, California) emerged as a new tool in the armamentarium against coronary artery disease. These novel devices demonstrated promising results in randomized studies (107) and are being progressively incorporated into routine clinical practice in Europe, the Middle East, and Asia (108–110). Bioresorbable vascular scaffolds are more conformable than metallic stents (111), and their struts, including those associated with ISA, are completely resorbed 2 to 3 years after implantation. This feature could potentially eliminate concerns related to very long-term metallic exposure to the coronary circulation in cases of delayed healing (i.e., ISA and noncoverage) (112,113). Whether the implantation of these novel devices can reduce adverse events related to late ISA compared with metallic stents in real-world populations warrants further investigation.

Another critical step in reducing late ISA, which is not directly procedure related, is the active search for polymers and antirestenotic drugs that continue to inhibit neointimal hyperplasia and induce less toxicity and inflammatory reactions in the vascular wall, resulting in less positive vascular remodeling. This “perfect equilibrium” between drug and/or polymer combinations has been pursued thoroughly by investigators over recent years in both pre-clinical and clinical trials with promising results in terms of reducing ISA (32,37,114–116).

### Table 2 Summary of Conclusions

<table>
<thead>
<tr>
<th>ISA is a multifactorial, morphological feature that is affected by procedure-related elements and by stent-vessel interactions over time.</th>
</tr>
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<tbody>
<tr>
<td>ISA is more commonly identified in DES than in BMS.</td>
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<tr>
<td>OCT is superior compared with IVUS in diagnosing ISA.</td>
</tr>
<tr>
<td>Although an association between ISA and adverse clinical events is strongly suggested by histopathology and in vivo studies, highly selected populations may introduce bias to these findings; therefore, ISA is the most likely 1 feature among several others that might predispose to ST.</td>
</tr>
<tr>
<td>The magnitude of acute ISA may predict its resolution and impact on vascular healing.</td>
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<tr>
<td>Standardization in data reporting and lesion-level assessment with the evaluation of clustering and heterogeneity could ultimately lead to a better understanding of ISA and its impact on clinical outcomes.</td>
</tr>
<tr>
<td>Particular clinical scenarios such as acute coronary syndromes, OLP stents, bifurcations, vessel tapering, and CTO are more prone to exhibit ISA.</td>
</tr>
<tr>
<td>Adequate stent sizing, optimal techniques of implantation, and intravascular imaging guidance can effectively reduce ISA rates.</td>
</tr>
<tr>
<td>Novel scaffolds such as self-expandable stents could play a role in reducing ISA because they can accommodate eventual positive vessel remodeling over time.</td>
</tr>
<tr>
<td>Finding antirestenotic drugs and/or polymers that cause less inflammation, and therefore, less positive remodeling, is another important aspect aimed at reducing ISA.</td>
</tr>
</tbody>
</table>

**CTO** – chronic total occlusion, **DES** – drug-eluting stent(s); other abbreviations as in Table 1.

### Conclusions

The main highlights of this comprehensive review are summarized in Table 2. ISA is a multifactorial, pathological feature, and although a clear cause-effect relationship with ST is still unclear, a body of data suggests that it might be one of the contributors in the prothrombotic vascular milieu. Optimal stent sizing and techniques of implantation, together with the use of new technologies, could minimize the occurrence of ISA.

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Key Words: drug-eluting stent(s) – incomplete stent apposition – intravascular ultrasound – optical coherence tomography – percutaneous coronary intervention – stent malapposition.