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EDITORIAL COMMENT

Incomplete Stent Apposition

Should We Appose or Oppose?*

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Incomplete stent apposition (ISA), also known as stent malapposition, is defined most simplistically as the absence of contact between stent struts and the vessel wall not overlying a side branch. Incomplete stent apposition can occur at the time of stent implantation—acute ISA—which might either resolve or persist at follow-up (late-persistent ISA). Patients without ISA at the time of stent implantation but in whom ISA is detected at follow-up are deemed to have late-acquired ISA. Stent underexpansion is defined as the cross-sectional area (CSA) of the stent compared with vessel size, either measured as mean reference-lumen CSA or lesion or reference-external elastic membrane CSA (1).

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A stent lumen area of <5.0 to 5.5 mm^2 on intravascular ultrasound (IVUS) has been associated with stent thrombosis (ST) and restenosis (2,3). The phenomenon of ISA is only detected by IVUS or optical coherence tomography (OCT), and there is no reliable angiographic surrogate. The frequency of acute ISA seems to be approximately 10% and is similar between bare-metal stents (BMS) and drug-eluting stents (DES) (4). The mechanism underlying acute ISA seems to be related to procedural technique and is most likely due to suboptimal stent implantation or severely calcified lesions, which do not allow for homogenous stent expansion (5). Late ISA is detected more often after DES (10% to 20%) than BMS (5% to 10%) implantation (5–7). There are multiple postulated etiologies for late ISA, including unrecognized ISA at time of stent implantation (late-persistent ISA), but late ISA seems to be predominately caused by 2 mechanisms (6–8). First, after stent implantation there might be an increase in vessel volume with minimal or no change in plaque volume, so-called positive remodeling; this is in all likelihood the most common mechanism underlying late ISA. Second, thrombus dissolution behind the stent might occur, which subsequently results in a gap between the stent and the vessel wall; this mechanism is most important after stent implantation in acute coronary syndromes (8,9). Therefore, the pressing questions are: Should we be concerned about ISA? And if so, should we be routinely screening for ISA? And if so, who should do the screening? How should it be managed?

In this issue of *JACC: Cardiovascular Interventions*, Steinberg et al. (10) provide further insight into the clinical implications of ISA. Existing data regarding the outcomes in patients with ISA are largely observational retrospective studies, and controversy exists regarding the clinical ramifications of ISA. Acute ISA has never been associated with adverse events, and the preponderance of data regarding late ISA demonstrates no association with adverse cardiovascular events at follow-up (6–8,11,12). However, some investigators have found that late ISA is associated with very late ST (9,13). Hoffmann et al. (6) reported pooled data from several sirolimus-eluting stent trials that showed that at 4-year follow-up subjects with late ISA had a similar incidence of major adverse events when compared with those without late ISA, suggesting no influence of late ISA on long-term clinical outcomes. These results are supported by several other studies that also demonstrated no association between late ISA and adverse clinical events, including death and ST (7,8,11,12). However, Cook et al. (9) evaluated consecutive patients presenting with very late ST with IVUS and found that, compared with IVUS from control subjects without very late ST, there was significantly more frequent ISA (77% vs. 12%, $p < 0.001$), suggesting that ISA might play a role in the pathogenesis of ST. A recently published meta-analysis using data from randomized trials found that late ISA was associated with very late ST, which seems to support the findings of Cook et al. (9). It is easy to see why so much controversy and contentious debate exist about the role of ISA in adverse events, specifically ST. So what are we to believe?

In the present study, Steinberg et al. (10) use pooled IVUS-substudy data from the several TAXUS trials to investigate the role of both acute and late ISA and future clinical events over long-term follow-up of 2-years. Of the 1,580 patients with IVUS studies both at stent implantation and at 9-month follow-up, there were 96 cases of acute ISA (6.0%) with no difference between BMS and DES and 36 cases of late ISA (2.7%) with more late ISA in the TAXUS (Boston Scientific, Natick, Massachusetts) moderate-release stent group (not commercially available stent platform) than BMS. Although the acute ISA frequency and lack of difference between BMS and DES seen in the present study are similar to previous reports (7,8,14), the rates of late ISA are significantly lower and could be explained by the fact that acute ISA was treated at the time of implantation with

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post-dilation and therefore not allowed to present as late-persistent ISA at 9-month IVUS follow-up.

With regard to acute ISA, the authors found that it had no impact on 9-month clinical events; this finding is consistent with all other previous reports (7,8,14) and suggests that acute ISA likely has no impact on short-term clinical outcomes. However, the major limitation to this and other like-designed studies is the lack of power to discriminate the risk of acute ISA.

Turning to the phenomenon of late ISA, the investigators found that during the 2-year clinical follow-up after the scheduled 9-month IVUS follow-up, major adverse cardiovascular events were comparable among patients with and those without late ISA. Again, these data are concordant with most previous studies investigating late ISA (6–8,11,12,14). In addition, the authors found that the late ISA seemed to result from positive remodeling without concomitant proportional abluminal neointimal growth, which is also consistent with numerous previous studies (6–8,11,12,14,15). The authors conclude that, on the basis of their findings, neither routinely detected acute ISA nor routinely detected late ISA is associated with adverse clinical events over long-term follow-up.

Steinberg et al. (10) should be commended on a well-performed analysis that provides additional information to the current body of literature evaluating ISA. However, as with any study there are limitations that we should consider before making definitive statements regarding ISA. First, the number of late ISA cases is small (n = 36) within this relatively large collection of pooled IVUS substudy patients, and therefore the number of cardiovascular events was exceedingly low, in fact no ST occurred in any patient with late ISA. Inadequate power is an important weakness of not just the present study by Steinberg et al. but all studies to date that have attempted to examine the clinical importance of ISA. It is exceedingly difficult to demonstrate an association between a relatively uncommon occurrence (late ISA) and an even rarer event such as very late ST. Second, the authors do not report the mean ISA area, which is important in understanding the severity of ISA. There is a continuum of ISA from "modest ISA found at routine IVUS follow-up," as stated by Steinberg et al. (10), and frank aneurysm formation, which has been associated with ST (16). In fact, in the study by Cook et al. (9), which found a high prevalence of ISA among consecutive patients with very late ST, the mean ISA area was extremely large (8.3 ± 7.5 mm^2) and nearly twice the minimum stent area of control subjects—this was not subtle ISA like that found in many of the previous studies, which found no association between ISA and ST (6–8,11,12,14). In fact, the study by Cook et al. (9) was a clinical IVUS study investigating a high-risk group—very late ST—that is unlike many of the previously published studies, including the current publication, which reported only data from randomized trials requiring routine follow-up IVUS in clinically stable patients. Therefore, it is plausible that modest ISA (<4 mm^2) is less likely to be clinically relevant as opposed to more severe ISA, which seems to be more likely to result in clinical sequelae.

It seems unlikely that a definitive randomized trial or a large enough observational registry will be performed that would help to determine whether ISA is clinically important. The infrequent nature of both ISA and ST, the need for routine IVUS follow-up, the long follow-up required to detect very late ST, and the exceedingly large number of patients required seem prohibitive. It seems that, on the basis of the current best-available published data, acute ISA is clinically unimportant, and the operator should focus on adequate stent expansion, not synonymous with ISA, which has been consistently associated with ST (2). Although plausible, there seems to be no definitive evidence linking modest degrees of ISA, such as reported by Steinberg et al. (10), and clinical events, namely ST. However, on the basis of limited observational evidence, there does seem to be an association between more severe ISA and ST (9,16). Whether to treat either modest or severe ISA by dilating the stent further remains unanswered. Obviously, further dilation of the stent carries minimal risk, and it might mitigate the future risk of ST.

Acute and late-acquired ISA is an IVUS phenomenon that is not definitively associated with adverse cardiovascular events, and until further exacting data are available, we should oppose the urge to appose routinely. The caveat to this opposition position would be in cases with egregious ISA, which we believe is very likely to also be associated with stent underexpansion and thus ST.

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