Acute and subacute stent thromboses have existed since the first stent implantation procedures. Initially recognized as a complication of brachytherapy, late stent thrombosis has become a public health issue only during the current era of drug-eluting stent (DES) implantation, as evidenced by the March 8, 2007, issue of the *New England Journal of Medicine*, which includes 5 articles, 2 perspectives, and 1 editorial discussing late DES complications.

**What Is Incomplete Stent Apposition?**

Incomplete stent apposition (ISA), synonymous with stent malapposition, is a lack of contact between stent struts and the underlying vessel wall not overlaying a side branch. ISA can be quantified by measuring the number of malapposed struts; the arc subtended by the malapposed struts; the distance between the malapposed struts and the vessel wall; and the area, length, and volume of the gap between the stent and vessel wall. ISA must be differentiated from and not confused with stent underexpansion. Stent expansion is the minimum stent area by itself or compared with a predefined reference. Although this distinction may seem obvious, ISA and stent underexpansion are used interchangeably by purported experts. Although the collaborative work of Nakamura and associates demonstrated an unexpectedly high percentage of IVUS-detected stent underexpansion and incomplete apposition after angiographically successful bare metal stent (BMS) implantations, no study has linked acute or subacute stent thrombosis to isolated acute ISA. Conversely, stent underexpansion has been a consistent finding in every IVUS study; for the most part, ISA in these patients either resolves and some persists. However, acute and persistent ISA after DES implantation is associated with less neointimal hyperplasia compared with acute ISA that resolves spontaneously. Although reendothelialization is below the resolution of IVUS, it is interesting to speculate that acute and persistent ISA also may be associated with reduced reendothelialization compared with acute and resolved ISA.

**When and How Often Does ISA Occur, and What Is Its Mechanism?**

ISA can be acute, occurring at the time of stent implantation, or late, detected at follow-up. Differentiating among the various types and presentations of ISA, specifically identifying the late and acquired variety, requires intravascular imaging (most commonly IVUS) both after stent implantation and at follow-up.

Acute ISA is mostly technique dependent and can occur after implantation of any type of stent. Acute ISA can resolve or persist; acute and persistent ISA can increase, remain stable, or decrease in size. It is not clear why some ISA resolves and some persists. However, acute and persistent ISA after DES implantation is associated with less neointimal hyperplasia compared with acute ISA that resolves spontaneously.

Late ISA, ISA detected at follow-up, can be late and acquired (occurring between implantation and follow-up) or acute and persistent as noted above. The mechanisms of late and acquired ISA are either positive remodeling (an increase in vessel dimensions) without an equal amount of persistent plaque or intimal hyperplasia growth so that the vessel pulls away from the stent (the most common mechanism) or plaque or thrombus dissolution so that a gap forms between the stent and the vessel wall (primarily in patients presenting with acute coronary syndromes). Although late and acquired ISA can occur after BMS implantation, brachytherapy treatment of BMS restenosis, radioactive stent implantation, and DES implantation, the exact underlying pathological mechanism responsible for positive remodeling remains unknown. Late and acquired ISA is a continuum from 1 malapposed stent strut to aneurysm formation. The frequency of late ISA appears to be greater after DES compared with BMS implantation depending on DES type, but it is less clear that the gaps between stent and vessel wall are larger after DES compared with BMS implantation, although aneurysm was rare in the BMS era. Like acute and persistent ISA, late and acquired ISA (whether after BMS or DES implantation) also is associated with less neointimal hyperplasia and presumably reduced reendothelialization. There are only 2 reports of patients with late ISA who underwent a second follow-up IVUS study; for the most part, ISA in these patients either remained stable or regressed during the second follow-up period.

**What Is the Diagnostic Accuracy of IVUS in Detecting ISA?**

There are no studies addressing this issue. It is assumed that IVUS detects significant ISA, missing only minor cases.
However, metallic stent struts are strong ultrasound reflectors, and excessive gain settings can exaggerate both reverberations and side lobes to obscure the gap between the struts and the vessel wall. In addition, thrombus formation and blood stasis can fill in this space, and IVUS thrombus detection is notoriously difficult. Documentation of ISA is enhanced by flushing saline or contrast from the guiding catheter to wash out static blood and/or to confirm the presence or absence of flow.

**How Predictive Is ISA for Late Stent Thrombosis?**

Although the IVUS literature has speculated that late and acquired ISA could lead to stent thrombosis, the report by Cook et al is the first to document this association convincingly. Let us examine their data in detail.

None of the patients with late stent thrombosis had baseline IVUS; therefore, it was not possible to differentiate acute and persistent ISA from late and acquired ISA. However, this may not be as important as the size of the stent–vessel wall gaps or the underlying pathology.

Late ISA was present in 10 of 13 late stent thrombosis patients and measured 8.3 ± 7.5 mm² in maximum cross-sectional area (range, 2 to 24 mm²), with 9 of 10 late stent thrombosis patients having a gap of ≥4 mm². To put this in perspective, the average late ISA area in the stent thrombosis patients in the study by Cook et al was greater than the average minimum stent area in these patients. Furthermore, this average late ISA area was twice the size of the average late ISA of the 21 control patients (4.0 mm²), the average late ISA area of the 7 slow-release and 10 moderate-release patients in the TAXUS-II trial (5.1 mm² and 3.4 mm², respectively), and the average late ISA area of 85 DES-treated patients reported by Hong et al (3.0 mm²)—none of whom had late sequelae. These were not subtle findings—cases of malapposition likely to be missed by IVUS and requiring more advanced intracoronary imaging techniques; they represented the extreme end of the spectrum, with 3 of 10 having frank aneurysms (lumen [stent + ISA] area >50% larger than the proximal reference), similar to the 2 patients reported by Feres et al who developed late stent thrombosis after follow-up IVUS detected marked late and acquired ISA.

What of the other 3 patients? One had a minimum stent area of 5.0 mm², and the other 2 had no IVUS-detectable explanation for late thrombosis. It is possible that ISA was missed because thrombus formation obscured the stent–vessel wall gap.

It has long been speculated that underexpansion and malapposition have a synergistic effect on stent thrombosis. Thus, the authors calculated a stent expansion index, dividing the minimum stent area by the reference lumen area, to show that stent expansion was less in late stent thrombosis patients compared with control subjects. Does this make sense? No, not in the conventional sense in which stents were underexpanded at implantation and underexpansion was detected only at follow-up. In fact, minimum stent area was similar between stent thrombosis and control patients. Instead, positive remodeling (increase in vessel dimensions), which was responsible for late and acquired ISA, probably affected the reference segments, causing an increase in vessel and lumen dimensions and artificially reducing the expansion index. This highlights the diffuse nature of this positive remodeling in these patients. It is not known whether a mere mismatch between an adequate absolute minimum stent area and a larger reference lumen area (rather than true underexpansion) contributes to stent thrombosis. However, the findings of Cook et al suggest a lessening of the impact of mechanical stent implantation problems on late stent thrombosis compared with acute/subacute stent thrombosis. Only 3 of 13 of late stent thrombosis patients had “real” stent underexpansion, a minimum stent area <5.0 to 5.5 mm² (a common criterion for DES underexpansion), fewer than have been reported with IVUS studies of acute/subacute thrombosis.

**Does ISA in and of Itself Cause Late Stent Thrombosis?**

In a recent article in this journal, Luscher and coworkers state, “We have shown that in humans delayed healing is common with current DES and that in those that thrombose, other factors, such as hypersensitivity reaction, bifurcating and ostial stenting, penetration of a necrotic core, stent malapposition, and restenosis, may also be important predictors of thrombosis.” I would turn this around to state that late ISA (whether acute and persistent or late and acquired) is common, occurring in 10% to 20% of DES, in patients who thrombose, other factors such as delayed healing, inflammation, and hypersensitivity must also play a role.

**Is This an Argument for Routine Use of IVUS?**

On one hand, it is possible to argue that routine IVUS during DES implantation will minimize stent underexpansion, uncovered edge stenoses, and acute ISA and that this will reduce restenosis, acute/subacute thrombosis, and perhaps the minority of cases of late stent thrombosis that can be attributed to implantation issues. It is also easy to argue that patients with clinical events should undergo IVUS in an attempt to determine the cause of DES failure, as was done in the study by Cook et al. However, it is harder to argue that routine baseline or follow-up IVUS will eliminate late thrombosis. First, late ISA is common, and the majority of IVUS-detected late ISA is not associated with clinical sequelae. Second, only rare cases of late thrombosis have had IVUS at implantation and/or prior follow-up. Third, the time for follow-up IVUS would be totally empirical. Fourth, the incidence of late stent thrombosis is low. Finally, what should the clinician do with this information? Although it is possible to dilate the stent further to decrease the magnitude of ISA, it may be impossible to abolish the large stent–vessel wall gaps reported by Cook et al and Feres et al. Furthermore, in some patients, late ISA may be progressive, or reestablishing stent–vessel wall contact may reinvigorate the process that produced positive remodeling and late ISA. Finally, it is not clear that merely reducing or even abolishing these gaps will eliminate late thrombosis.

**What Next?**

IVUS data are available in only a minority of patients in multicenter trials, in part because most of these trials included...
only a small IVUS substudy but also because of poor investigator compliance within the substudy. With the notable exception of TAXUS-II (in which IVUS was the primary end point and therefore was performed in 85%13), follow-up IVUS adequate to detect late ISA was available in only 40% of patients in RAVEL,20 15% of patients in SIRIUS,12 and 20% of patients in an integrated analysis of TAXUS-IV, V, and VI. Paired (postintervention and follow-up) IVUS, necessary to detect late and acquired ISA, was done in even fewer patients. Among these multicenter studies, there were <100 patients with late ISA, and only half of them had late and acquired ISA. The single-center study by Hong et al8 alone contained 133 patients with late ISA, 82 of whom had late and acquired ISA. Importantly, none of these studies reported late stent thrombosis in any late ISA patient either at the time of detection or during subsequent clinical follow-up, although the size of the ISA was similar to that in the control group in the study by Cook et al.

The report by Cook et al11 raises as many questions as it answers. It is possible to conceive of a study that would answer some of these questions: baseline (blinded) IVUS, routine IVUS follow-up with randomization of late ISA patients to additional stent expansion versus no intervention, and subsequent clinical follow-up with IVUS imaging of patients presenting with late events. Given the relative infrequency of each event, the difficulty in collecting comprehensive data (particularly the required IVUS data), the “modest” reported size of late ISA in large prospective studies, and the protracted follow-up that would be necessary, the number of patients and the time course would be daunting. For now, we must rely on important observations such as the study performed by Cook and colleagues that provide insights into this clinical problem, and the question of whether identifying and treating late ISA will reduce late stent thrombosis remains unanswered.

Disclosures
Dr Mintz is a member of the speakers’ bureau for Boston Scientific Corp and is a consultant for and shareholder of Volcano Corp.

References

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