Patients undergoing percutaneous coronary intervention with a conventional bare-metal stent often require treatment for restenosis within 6 months of initial treatment due to neointimal hyperplasia. Drug-eluting stents (DES) have been developed for patients undergoing repeated treatments at short intervals because restenosis becomes refractory. DES have emerged as devices that can dramatically reduce the incidence of restenosis. However, there are concerns about the risk of stent thrombosis increasing because DES inhibit vascular smooth muscle cell proliferation and delay re-endothelialization. Once stent thrombosis occurs, it frequently causes serious complications including myocardial infarction and cardiac death. The greatest concern with DES is very late stent thrombosis (VLST), which occurs >1 year after DES implantation.

Another issue is that the incidence of stent thrombosis does not decrease during the extended follow-up period. According to Academic Research Consortium (ARC) definitions, the Bern–Rotterdam registry indicates that the incidence of definite stent thrombosis increases at a rate of 0.6% per year between 30 days and 3 years after stenting, with 3-year cumulative incidences being 2.9%. Increase in the incidence of stent thrombosis did not show a tendency of decreasing even after 3 years, indicating a persistent risk. The J-Cypher Registry shows the clinical outcomes of first-generation DES, sirolimus-eluting stent (SES). This multicenter, prospective registry is designed to evaluate real-world outcomes reflecting the clinical entity in Japan by enrolling consecutive patients with SES, including those with off-label indications. The result demonstrated that the incidences of ARC-defined definite stent thrombosis were 0.35% at 30 days, 0.59% at 1 year, 0.78% at 2 years, and 1.2% at 3 years. These incidences are lower than those expected from the complex demographic and lesion characteristics of the patient population in the J-Cypher Registry, but are similar to results from reports worldwide, including the Bern–Rotterdam registry in which the incidence of stent thrombosis increased at a rate of 0.29% per year without showing a tendency of decreasing during the 3-year follow-up period.

In this issue of the Journal, Kim et al reported a relationship between the incidence of coronary artery aneurysm (CAA) after DES implantation and the onset of related clinical events. CAA was identified by coronary angiography in 1.7% of patients, mostly >1 year after DES implantation. In 14.3% patients with CAA, DES implantation was associated with significant clinical stent thrombosis. DES implantation in lesions responsible for myocardial infarction has been identified as the most powerful predictor of CAA. This report is significant because it demonstrated a relationship between CAA formation and stent thrombosis, and identified the predictor of CAA formation. Another study using intravascular ultrasound (IVUS) also indicated that CAA, identified in 1.25% patients, commonly developed after stent implantation in the culprit vessel in acute myocardial infarction. A previous study reported that similar to CAA, late-acquired incomplete stent apposition (late-acquired ISA), which represents poor stent strut contact with the vessel wall, is also associated with VLST. An additional report showed that the onset of late-acquired ISA is common in the culprit vessel in acute myocardial infarction. A result of retrospective analysis of patients with stent thrombosis in the RESTART registry (the largest stent thrombosis registry) is interesting. In this registry, data accumulated from 611 patients with ARC-defined definite stent thrombosis (322 with early [within 30 days], 105 with late [between 30 days and 1 year], and 184 with very late [≥1 year] stent thrombosis) have been analyzed. Kozuma et al reported that 37.6% of patients experiencing VLST showed peri-stent contrast staining (PSS) on angiography at the onset. He defined PSS as contrast staining outside the stent, and representing the onset of delayed incomplete apposition of stent struts to the vessel wall.

Pathological reports demonstrated that inflammatory response occurrence in the vessel wall in a DES-implanted lesion is more severe when DES is implanted in the culprit vessel in acute myocardial infarction. The mechanism of VLST development involves a hypersensitivity reaction induced when a polymer (a constituent component of DES) is recognized as a foreign substance after implantation. The resultant inflammation alters the vessel wall structure, causing positive remodeling. Vessel wall destruction leads to CAA formation in extreme cases. Relatively milder inflammatory changes are recognized as PSS on coronary angiography and as late-acquired ISA on IVUS, or optical coherence tomography. In any case, occurrence of a severe inflammatory response, including cosinophilic infiltration, in the local lesion may result in stent thrombosis, with contributions from modulators such as surgery and discontinuation of antiplatelet drugs.

Speculative Mechanisms for Very Late Stent Thrombosis After Drug-Eluting Stent Implantation
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Incomplete stent apposition, which is found by some method during follow-up after satisfactory contact of the stent with the vessel wall has been documented immediately after DES implantation, is expressed using several terms, characterized by the following 3 phenomena: CAA, PSS, and late-acquired ISA, in probable descending order of distance or space between the stent and vessel wall. These have been defined in articles addressing each individual phenomenon, but their consensus-based definitions have not been established. Unifying the definitions of these terms is desirable for comparison of their incidences or to discuss the incidence of clinical events attributable to them because this is expected to allow data comparison and contribute to the understanding of their mechanisms.

VLST is the greatest concern with DES, but there is emerging hope for a solution to this concern. A report of the COMPARE trial indicated that a second-generation DES, the everolimus-eluting stent, causes early and late stent thrombosis less frequently than the conventional, first-generation DES. In addition, a 2-year follow-up of the COMPARE trial reported significantly less frequent VLST (oral presentation by Smits at the Annual Scientific Meeting of the Transcatheter Cardiovascular Therapeutics 2010, Washington DC, USA). Moreover, it has been postulated that VLST pathogenesis may involve an immune reaction to durable polymers, but the next-generation Nobori Biolimus A9-eluting stents use biodegradable polymers. Long-term follow-up data regarding the contribution of the new polymer in reducing VLST incidence are awaited.

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