A Culprit in Very Late Stent Thrombosis

Aloke V. Finn, MD; Fumiyuki Otsuka, MD

Since the advent of balloon angioplasty in the 1970s by Andreas Gruntzig, restenosis, or the excessive proliferation of smooth muscle cells into the intima, has been regarded as the primary limitation of percutaneous coronary intervention. The introduction of bare metal stents (BMS) in the 1990s reduced restenosis rates by eliminating elastic recoil and negative remodeling, and represented a significant advance. If one could escape the early risk of vessel narrowing within the first 12 months after implantation, long-term outcomes appeared to be favorable, with late increases in luminal diameter between 1 and 3 years.1 However, data from a series of reports, including 1 in this issue, suggest the cellular response to stenting is a complex and dynamic phenomenon, not detectable by traditional luminography, that continues to evolve many years after stent placement and may be an important cause of late thrombotic events. These data enhance our understanding of how and why thrombosis within stents sometimes can occur late, many years after percutaneous coronary intervention.

Article see p 47

Unlike angioplasty, stenting results in prolonged chronic inflammatory cell recruitment.2 In a series of human autopsy implants, Inoue et al3 reported that important temporal changes occur in the neointima after BMS placement in humans. Arteries that had been stented for 2 to 3 years demonstrated endothelial coverage with smooth muscle and collagen rich neointima. Chronic inflammation was observed and was characterized by macrophages, T cells, and giant cell infiltration. In stents implanted greater than 4 years, smooth muscle cells were sparse, with abundant collagen toward the lumen and evidence of foamy macrophages (so called “neoatherosclerosis”) around stent struts, which expressed metalloproteinases. These data suggest that neointima formation that occurs after metallic stent implants is subject to the same atherosclerotic forces that affect native vessels, and that macrophage mediated degradation of collagen eventually could result in necrotic core formation, and possible rupture and thrombosis.

More recently, we reported similar findings in a series of bare metal stent implants with comparable temporal associations.4 Stents ≤2 years demonstrated no evidence of neoatherosclerosis, whereas there was a progressive increase in its incidence in stents >2 but ≤6 years (22%), and in those >6 years old (42%). It is important to note that while these changes were present in a fair number of stents, the incidence of an unstable type of plaque morphologies were much lower, representing 4% of all stents examined, with none present in stents ≤2 years old. The latter data are consistent with the reported clinical late thrombotic event rates after BMS placement, which hover in the range of 0.1% per year.5

While data from autopsy findings can lend insights into problems such as these, issues of selection bias commonly are raised, calling into question the representative nature of such investigations. This is where clinical studies, such as the one conducted by Yamaji et al6 in this issue of Circulation: Cardiovascular Interventions, complement and enhance information obtained from autopsy. The authors examined thrombectomy specimens from a series of 135 patients undergoing angiography and thrombectomy for definite stent thrombosis after BMS placement. Extracted thrombi (under negative pressure) were histopathologically evaluated and compared according to the timing of stent thrombosis (ie, early ≤30 days, late >30 days, ≤365 days, and very late >365 days). Fragments of atherosclerotic plaques, including foamy macrophages, cholesterol crystals, and thin fibrous caps, were seen more commonly in cases of early and very late stent thrombosis beyond 3 years, as opposed to late stent thrombosis, and were similar to what was retrieved in acute coronary syndrome cases. These results suggest that disruption of neoatherosclerotic plaque may be an important cause for late, and especially, very late thrombotic events after BMS placement.

While these results also seem to suggest different causation for late and very late thrombotic events after BMS placement, some limitations of the present analysis also must be pointed out. Obviously, the nature of the thrombectomy technique does not allow us to determine the exact location where extracted plaque elements originated. Rupture of de novo atherosclerotic plaque both proximal and distal to the stented segment cannot be excluded as the source of thrombectomy material (Figure 1). Indeed, previous pathology studies have suggested this as an important mechanism of late bare metal stent thrombosis.7 In addition, some inconsistencies with previous autopsy data of Nakazawa8 also are present. Yamaji et al6 report that 10% of stents with evidence of late (ie, >30 days and ≤365 days) thrombosis demonstrated neoatherosclerotic changes with advanced plaque morphologies. Stents implanted >365 days but ≤3 years demonstrated no evidence...
of neoatherosclerosis, while those >3 years again showed neoatherosclerotic change. In contrast, Nakazawa et al reported no evidence of neoatherosclerosis or unstable plaque morphology in any BMS implanted ≤2 years of age (Figure 2). A potential explanation for this discrepancy is the possibility that what was sampled by Yamaji was in fact either fragments of native plaque (from negative pressure) underlying the stented segment, or more likely plaque from the proximal or distal nonstented segments of the artery (Figure 1). Only intravascular imaging prior to thrombectomy would have settled this issue.

What seems more reliable in this analysis is the data that suggests the incidence of neoatherosclerosis increases with age of the stent, especially after the 3-year mark. These findings are concordant with those of Nakazawa and Inoue, and suggest that thrombotic events occurring 3 years after BMS placement seem more likely to be attributable to neoatherosclerotic change (Figure 2). Because neoatherosclerosis is rarely present in BMS less than 1 year old, late thrombotic events occurring in this time period are likely caused by other factors. Farb et al described pathological mechanisms of late bare metal stent thrombosis occurring after 1 to 11.9 months. Purported mechanisms were bifurcation stenting, stent placement within an existing necrotic core rich lesion, extensive plaque prolapse, plaque rupture proximal or distal to the stented segment (Figure 1), and occlusive restenosis. While in the study by Yamaji lesion characteristics were not different between cases of late and very late stent thrombosis, the overall numbers in this series are small, and it seems likely that at least some of these mechanisms could account for the differences in thrombectomy aspirates seen.

This and other studies also shed light on recent data regarding late thrombotic events after drug eluting stents (DES), now the dominant device used in coronary interven-
While late DES thrombosis has been most associated with delayed healing, described as incomplete endothelialization of the stented segment, more recent data seem to support the contention that neoatherosclerosis with neointimal rupture is another important cause. Pathological studies suggest that atherosclerotic change occurs more quickly in DES versus BMS (420 days versus 2160 days), and thus neoatherosclerosis must be considered as a cause of DES thrombosis even in stents 2 years of age. Why DES neoatherosclerosis is accelerated remains unknown, but it is tempting to speculate that dysfunctional porous endothelium contributes heavily to this process. Animal studies support that incomplete maturation of the regenerated endothelium with poorly formed cell junctions are more frequently observed in DES as compared with BMS. In 50 DES restenotic lesions on average 32 months old, Kang et al recently showed that 52% had in-stent features of vulnerable plaques and 58% had evidence of neointimal rupture, as detected by optical coherence tomography and intravascular ultrasound. Multiple studies have now confirmed that first generation DES demonstrate a continued rate of very late stent thrombosis (0.26% to 0.4%/yr), with little evidence of a plateau up to 5 years. To what extent these events are caused by neoatherosclerosis remains unknown, but certainly deserves further investigation.

Collectively, these data reinforce the need to continue to understand the complexity of the biological responses to intravascular devices, especially as technology advances faster than potential adverse consequences can be anticipated. As in the process of native atherosclerosis, inflammation seems to play an important role in long-term reaction to stent placement, with significant clinical consequences for some patients, especially restenosis. Importantly, the factors that predispose individuals to neoatherosclerotic change remain unknown, but endothelial incompetence and activation may be involved. What is clear is that we need to understand better how to minimize this type of adverse device related consequence in order to improve the safety and durability of intracoronary stents.

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**References**


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