In-Stent Atherosclerosis at a Crossroads

Neoatherosclerosis … or Paleoatherosclerosis?

Ioannis Andreou, MD, PhD
Peter H. Stone, MD

Accumulating histopathologic and intravascular imaging studies indicate that atherosclerosis development inside a coronary stent is a complication that may be identified as the substrate in a considerable proportion of late/very late stent thrombosis and restenosis cases.[1] The frequency of in-stent atherosclerosis-related very late stent thrombosis is similar between early and new-generation drug-eluting stents but with considerably shorter implantation-to-thrombosis interval in the latter.[2] Although in-stent atherosclerosis has recently been the subject of continued concern and investigation, the mechanisms of its development remain unknown. The prevailing hypothesis is that it occurs due to the formation of de novo atherosclerosis within the neointima, which has led to the widespread adoption of the term "neoatherosclerosis." However, the underlying native atherosclerotic plaque might as well contribute to the pathogenesis of this disease entity, a hypothesis largely overlooked in recent reports.

Our current understanding of in-stent atherosclerosis derives solely from pathological and retrospective observational clinical studies, which only provide a single snapshot of atherosclerotic lesion evolution. The term "neoatherosclerosis" has been adopted on the assumption that the atherosclerotic tissue within the stent does not communicate with the underlying native atherosclerotic plaque (ie, de novo atherosclerosis). However, whereas in autopsy studies it may be feasible to identify lesions without evidence of direct communication between the underlying plaque and overlying neointima, likely signifying neoatherosclerosis development, clearly the currently used intravascular imaging modalities, mainly optical coherence tomography, cannot discriminate between the 2 hypotheses concerning the preceding pathobiologic mechanism. This fact may account, at least partly, for the substantially conflicting data on the prevalence and complications of in-stent atherosclerosis between autopsy and clinical optical coherence tomography studies, both reported much higher in the latter studies.[1]

What is the evidence for de novo in-stent atherosclerosis development? A suggested explanation for the neoatherosclerosis hypothesis has been that neointima transforms into atherosclerotic tissue primarily due to delayed or impaired reendothelialization after poststent endothelial denudation.[1] Indeed, drug-eluting stents not only target vascular smooth muscle cells but also endothelial cells, resulting in incompetent endothelial coverage of the stented segment with poorly formed intercellular junctions favoring a greater lipid diffusion and inflammatory cell migration into neointima. However, it needs to be noted that this mechanism would not apply to bare metal stents that may develop atherosclerosis very late after their placement despite complete endothelial coverage within 3 to 4 months. Neoatherosclerosis formation could also be promoted by the development of small regions with flow reversal and disturbed shear stress between nonstreamlined stent struts, contributing to the continued activation of the regenerating endothelial cells toward a proinflammatory phenotype. Again, one could speculate that disturbed shear stress might also contribute to the progression of the underly-

Correspondence to: Ioannis Andreou, MD, PhD, 75 Francis St, Brigham and Women's Hospital, Harvard Medical School, Cardiovascular Division, Boston, MA 02115. E-mail yannisand@yahoo.com

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ing native plaque. Moreover, persistent stent metal/polymer-evoked foreign body inflammatory response and subsequent neovessel formation leading to macrophage recruitment might enhance neointimal atherosclerotic changes. Nevertheless, atherosclerosis development within the neointima has been reported even after bioresorbable vascular scaffolds or drug-coated balloons, which avoid the proinflammatory effects of stent struts.[3] Collectively, although the neoatherosclerosis hypothesis has a sound theoretical basis, it remains controversial and unproven.

What happens with the native plaque after stent implantation? An alternative and potential complement to the previous hypothesis is that the underlying native plaque plays an important role in the development of in-stent atherosclerosis. During stent deployment, the vascular wall undergoes significant expansion triggering an inflammatory response and leading, among others, to the compression of the plaque. In the absence of a potent antiatherosclerotic-eluted drug, this plaque might evolve over time or be a source for cells, growth factors, and chemoattractant chemokines and cytokines, contributing to in-stent atherosclerotic process. In support of this concept, we have shown in a serial intravascular ultrasound study that the decrease in atherosclerotic plaque area located behind the stent over time is significantly associated with the magnitude of neointimal development at follow-up, raising the possibility of a communication between the lesion within the stent and the underlying native atherosclerotic plaque with potential tissue shifts across the stent struts.[4] Constrictive arterial remodeling that often occurs after stenting might significantly contribute to this process.[4] Furthermore, stent implantation is almost invariably associated with varying degrees of tissue protrusion.[5] Accordingly, because plaque may be squeezed through the stent strut interstices, atherosclerotic foci could remain and progress within the intima overlying the struts immediately poststenting that might erroneously be presumed as neoatherosclerotic at autopsy or intravascular imaging at follow-up. In this context, the presence of unstable

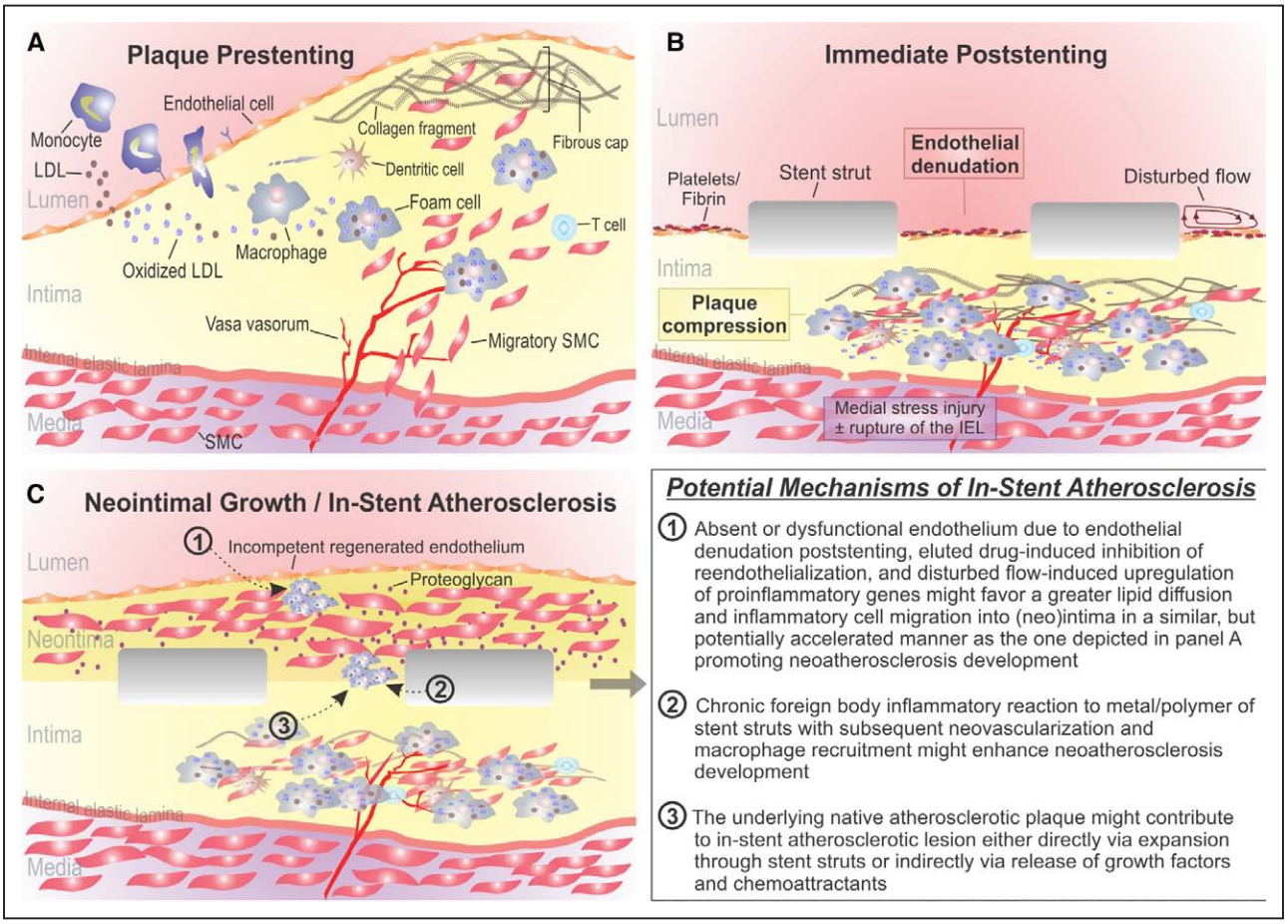

Figure. Potential mechanisms of in-stent atherosclerosis development.
A, Coronary atherosclerotic plaque development before stenting. **B**, Immediate result of stent deployment with endothelial denudation, disturbed local blood flow patterns, and underlying native plaque compression. **C,** Mechanisms of atherosclerosis development within the neointima (identified with circled numbers) months to years after stenting. IEL indicates internal elastic lamina; LDL, low-density lipoprotein; and SMC, smooth muscle cell.

underlying lesion morphology has been reported to be a significant predictor for the development of in-stent atherosclerosis in autopsy studies.[1] Moreover, a recent optical coherence tomography study reported that significant poststenting tissue protrusion is an independent predictor of target lesion revascularization.[5] Intriguingly, an example case of this study demonstrated that the location of intrastent tissue protrusion at postintervention well matched that of neointima at follow-up.[5] Taken together, several lines of indirect evidence implicate the underlying native plaque in the pathogenesis of in-stent atherosclerosis.

The identification of in-stent atherosclerosis pathomechanisms remains highly challenging (Figure). It is plausible that both hypotheses hold true, and the prevalence of underlying mechanisms differs according to stent type (eg, drug-eluting vs bare metal stents) or atherosclerotic foci location (eg, adjacent to the luminal surface vs adjacent to the struts). The discrimination between neoatherosclerosis and paleoatherosclerosis (ie, progression of preexisting disease) could be of clinical significance assuming their potential different outcomes and treatment strategies. A better understanding of the underlying processes could lead us to refinements in stent design and targeted antiatherosclerotic therapies of this emerging indicator of high-risk stents. Prospective cohort studies and increasing sophistication in coronary imaging to improve tissue characterization around the implanted stent will be fundamental to advancing the understanding of the mechanisms and natural history of in-stent atherosclerosis in the future.

DISCLOSURES

None.

AFFILIATIONS

From Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (I.A., P.H.S.); and Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge (I.A.).

FOOTNOTES

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