Late Stent Thrombosis After Drug-Eluting Stent
Seeing Is Understanding
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Following the inspiration of Dr S. Windecker, the team from Bern, Switzerland, has contributed >30 studies on drug-eluting stent efficacy and safety, several of which represent essential pieces in the puzzle. The article in this issue of Circulation by Cook et al1 belongs to that select group of key references. The series of robust and detailed reports on the Bern-Rotterdam cohort studies have coined the 0.6% yearly linear rate of definite late stent thrombosis associated with the permanent coronary implantation of first-generation drug-eluting stents.2 Intravascular ultrasound imaging of the thrombosed stents has revealed the strong association of incomplete strut apposition with the event.3 At the same time, collective analysis of all the available evidence4 demonstrated that a reduction in restenosis with drug-eluting stents prevented adverse events caused by the treatment of the more frequent recurrences with bare metal stents. With the former compensating for the latter, the net result of this balancing act between safety and efficacy resulted in no difference in death and myocardial infarction rates up to 4 years after the initial procedure.

Study Findings
In the present study, late hypersensitivity reaction was identified as a cause for late stent thrombosis, in association with stent malapposition caused by necrotizing vasculitis around the stent struts. Histopathological analysis of aspirated thrombus showed eosinophilic infiltration typical for type IVb hypersensitivity reaction following implantation of sirolimus-eluting stents. Macrophage infiltration typical for type IVc hypersensitivity was seen with paclitaxel-eluting stents. The biomarker gradient between coronary and peripheral blood was significant for high-sensitivity C-reactive protein and myeloid-related protein 8/14, both markers of local inflammatory reaction. These patterns were not observed with early drug-eluting stent thrombosis, early and late thrombosis of bare metal stents, or coronary thrombosis causing wild-type myocardial infarction.

As Cook et al mentioned, previous studies have shown rare systemic allergic reactions, and autopsy studies have shown eosinophilic infiltration around struts and polymer remnants after late sirolimus-eluting stent thrombosis. In addition, 1 case report of severe systemic allergic thrombosis was associated with positive cardiac gallium scintigraphy, a marker of macrophage infiltration, which was reversible after steroid treatment.5 Such systemic reactions are extremely rare, but Cook et al now confirm that local hypersensitivity reactions are the more likely mechanism of (very) late stent thrombosis through excessive positive remodeling, 2 rare unwanted effects specifically associated with permanent implantation of first-generation drug-eluting stents.

New Answers
These findings eventually clarify many of the unresolved issues and controversies surrounding the topic. The seemingly erratic pattern of (very) late stent thrombosis, the steady linear increase over time with no evidence of decreased event density with extended follow-up, and the weak association with discontinued dual antiplatelet therapy (in contrast to early thrombotic events) are all consistent with the evoked mechanism of action. Despite the small number of observations, a strong relation was observed between the extent of stent malapposition by intracoronary ultrasound imaging and the degree of eosinophilic infiltration. Whether malapposition per se is sufficient to trigger thrombosis is unclear. Some previous reports have failed to identify a relationship between malapposition and major adverse cardiac events.6 However, these studies have not focused on late events, and in addition to necrotizing vasculitis, malapposition can be the result of initial stent underdeployment or resolution of mural thrombus jailed between the vessel wall and the stent struts at the time of initial delivery. As alluded to by the authors, inflammatory cells release prothrombotic factors, and hypereosinophilia is associated with increased platelet activation and propensity for thrombosis. It is thus possible that mostly stent malapposition caused by local hypersensitivity reaction represents the pathogenetic substrate for late thrombosis events.

New Questions
As with any great study, this one raises many new questions. It is unclear to what extent delayed hypersensitivity events are embedded in earlier stent thrombosis cases. Obviously, the present mechanism reveals when other causes of stent thrombosis directly related to procedural factors or inappropriate antiplatelet therapy are exhausted. It is tempting to incriminate polymers and their imperfect biocompatibility. In theory, the fact that sirolimus is long gone at the time of (very) late stent thrombosis does not completely rule out delayed hypersensitivity to the drug. However, late hypersensitivity involves primarily T cells, which are suppressed by...
sirolimus. Late appearance of the reaction is compatible with the reaction being caused by polybutyl methacrylate in the case of sirolimus-eluting stents or styrene-isobutylene-styrene triblock in the case of paclitaxel-eluting stents. Other nanocomponents of the devices could equally be blamed. What are the practical consequences of these findings for the many carriers of these stents? Probably none, especially when the hypersensitivity reaction remains localized to the coronary circulation. Desensitization is not an option. Removal of the sensitizing agent would be ideal, which is not an option either with these permanent implants. Steroids can be used when systemic inflammatory signs are present. Whether extension of dual antiplatelet therapy with either clopidogrel or prasugrel beyond 1 year confers any protection against (very) late stent thrombosis is unknown and is now being tested prospectively in the United States as mandated by the Food and Drug Administration. Even when shown to be efficacious, the cost-utility of this therapy will be rather unfavorable given the rarity of the thrombosis event and the significant bleeding risk with extension of the therapy. Currently, patients can simply be reassured that the net balance of effects favors drug-eluting stents despite the very small risk of late stent thrombosis.

Impact on Approval Processes for New Drug-Eluting Stents

It would seem obvious that the optimal pathway to resolve the issue is to design new drug-polymer-device iterations that are devoid of the late-hypersensitivity side effect. From this perspective, it is unlikely that even the most extensive preclinical testing will ever provide any certainty. Given the permanent nature of this specific implant and the requirements for global biocompatibility and compatibility with blood constituents, it may be wise to narrow the search to polymers and drugs that have been used extensively in humans for other indications with known outcomes. Regulatory authorities also should realize that continuously raising the bar for approval of new options is counterproductive. Such strategy is driven by a precautionary attitude that eventually leads to an undesirable prolongation of the life cycle of the earlier devices, precisely the ones that are fraught with unwanted childhood diseases.

Future Research

In addition to the search for the optimal drug-polymer-device iteration, there is a need for future collaborative research on this topic. Studies similar to this one are needed to increase the number of observations and to expand the knowledge to all carriers of these stents? Probably none, especially when the local nature of the processes, this may not be feasible, although encouraging data have recently been reported by Niccoli et al.7 Baseline plasma levels of eosinophil cationic protein, a marker of eosinophil activation, were shown to be predictive of future events after stent implantation. Several candidate markers addressing macrophage or T-cell activation could equally be studied sequentially. Given the strong association between hypersensitivity and late acquired stent malapposition, invasive imaging observations could easily be correlated with biomarker findings. Although stent thrombosis is rare, malapposition is not an infrequent finding, seen in 8% to 13% of patients 9 to 12 months after implantation of first-generation drug-eluting stents. Linking this phenotype to biomarker changes may help to identify patients at risk of late stent thrombosis, perhaps the patient subset that will benefit from long-term dual antiplatelet therapy.

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