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EDITORIAL

Platelet activation and stent thrombosis

Coronary stent thrombosis remains a severe complication after coronary interventions. The incidence of early stent thrombosis is <1%, and the rate of stent thrombosis in up to 1-year follow-up ranges from 0.6% to 3.4%.[1] Although the use of drug-eluting stents (DES) is associated with significantly lower rates of restenosis than bare-metal stents (BMS), the incidence of early and late stent thrombosis is similar between DES and BMS. However, very late stent thrombosis, although uncommon, occurs more frequently in first-generation DES.[1]

The mechanisms underlying stent thrombosis are multifactorial, including patient-related (diabetes, advanced age), lesion-related (long lesions, bifurcation lesions), procedural (multiple stents, stent malapposition), and post-procedural factors (non-compliance, premature cessation of anti-platelet treatment).[2] Platelets are known to play a major role in thrombus formation in the coronary stent. The coagulation system has also been implicated to the pathophysiology of stent thrombosis. Before re-endothelisation, BMS and DES stent struts, and/or polymer material, may induce platelet adhesion, activation and thrombus formation, leading to early stent thrombosis. Cytotoxic drugs used in DES to reduce smooth muscle cell growth after coronary intervention also inhibit this endothelialisation.[2,3] In addition, sirolimus and paclitaxel induce the expression of tissue factor in the stented lesion causing the activation of the extrinsic coagulation cascade. Delayed endothelial coverage, persistent fibrin deposition, and ongoing vessel inflammation are associated with thrombosis after stent implantation and are likely responsible for the higher rates of very late thrombosis occurring with first-generation DES.[4,5]

The thrombogenicity of DES compared with that of BMS is an on-going debate. In particular, sirolimus has been associated with thrombocytopenia, impaired fibrin formation or impaired fibrinolysis and with agonist-induced platelet aggregation in a time- and dose-dependent manner.[6]

In this context, Marketou et al sought to investigate the behaviour of platelet activation markers and coagulation proteins after sirolimus-eluting stent (SES) implantation, comparing the results with those after BMS implantation up to 6-months follow-up.[7] They studied 47 'low-risk' patients with stable coronary artery disease who received standard pre-procedural anti-platelet therapy. They observed a significant time effect ($p<0.001$) on the von Willebrand factor (vWF), ($p=0.012$) factor VIII, sP-selectin ($p=0.04$), b-thromboglobulin ($p<0.001$), and platelet factor 4 levels ($p=0.016$) and a significant stent-effect ($p<0.015$) only on vWF levels.[7]

Several studies have reported on enhanced post-stent platelet activation, as measured by increased circulating markers or increased expression of cellular molecules on platelets.[8,9] Restricted patient numbers and absence of systematic detection limit the results. The study of platelet functions is always hampered by differences in the methodological variables used. The analysis of such data is also limited by the potential impact of unidentified confounders. Heterogeneities of study groups regarding basic clinical characteristics, angiographic and stent procedure-related parameters, anti-coagulation treatment, and even operator skills may influence the results. Nonetheless, a consistent finding is the significant platelet activation in the early phase after stent implantation, emphasising the need for more effective anti-platelet strategies at this time.

This is further complicated by the interaction of activated platelets with the thrombogenic surroundings of stent deployment. Several coagulation markers that are closely related not only to the haemostatic effects of platelets but also to the development of atherosclerotic plaques have been investigated. The post-stent hypercoagulable profile of patients has been confirmed by most investigators. However, a sub-group analysis according to different stent types used is difficult to perform because of the small numbers of patients enrolled. Some reports in patients with stent thrombosis have detected altered plasma fibrin clot properties associated with attenuated fibrinolysis, with no differences in the levels of fibrinogen and regardless of platelet reactivity.[10]

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The vWF is a well-characterised marker of endothelial dysfunction, which plays a central role in platelet adhesion and aggregation under high shear conditions, (i.e. at the sites of lesions in the coronary arteries) and in fibrin clot formation by acting as a carrier protein for factor VIII.[11] Stent implantation, and especially in the case of multiple coronary stenting, is associated with endothelial damage and concurrent mechanically induced vWF release. Consistent with previous results, Marketou et al observed lower increase in vWF concentrations after SES than those after BMS, reflecting a reduced inflammatory response.[7] Contrary to the BMS group, vWF levels at 6 months were still above baseline in the SES group, probably due to delayed endothelisation and persistent fibrin deposition.[7]

Optimal stent deployment techniques, new stent designs and improved anti-thrombotic therapy are the recommendations for avoiding stent thrombosis. Further large-scale studies and prolonged follow-up should be performed to illustrate the independent and complementary prognostic value of biomarkers for adverse events such as stent thrombosis and restenosis. Thus, new drug development and advances in applied pharmacotherapy may significantly improve both the short- and long-term success rate of percutaneous transluminal coronary angioplasty.

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