Lost contact with vessel wall, signed contract with stent thrombosis?

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This editorial refers to ‘Impact of incomplete stent apposition on long-term clinical outcome after drug-eluting stent implantation’, by S. Cook et al., on page 1334

Drug-eluting stents (DES) represent the most successful approach in preventing restenosis after percutaneous coronary interventions (PCIs). Many believe, however, that reduction of neointima formation is associated with a worrisome side effect, an increased risk of very late stent thrombosis, at least as observed with early DES technologies. An adverse vessel wall reaction to two DES components—drug and polymer—has been called into question.

On balance, an increased risk for very late stent thrombosis seems to be the price to be paid for the dramatic reduction of restenosis with DES of earlier generations. A similar therapeutic imperfection related to PCI also exists for the adjunct antithrombotic therapy; an increased risk of bleeding is the price still to be paid for the prevention of stent thrombosis. Thus, identification of that very small fraction of patients carrying an excessive risk of DES thrombosis, and probably requiring prolonged dual antiplatelet therapy (DAPT), has the potential of minimizing exposure to an increased risk of bleeding.

A multitude of studies have been dedicated to the assessment of factors predictive of DES thrombosis. Premature discontinuation of ADP receptor antagonists has emerged as one of the most prominent predictors, although little is known about the optimal duration of DAPT after DES. Certain clinical and lesion characteristics along with a poor platelet response to clopidogrel have also been identified as correlates of DES thrombosis risk. Another direction of investigations is based on intravascular imaging techniques. A new parameter, late incomplete stent apposition (ISA), has attracted the attention of both intravascular ultrasound (IVUS) and optical coherence tomography (OCT) studies as a candidate predictor of late DES thrombosis. Incomplete stent apposition refers to proof by imaging of the lack of strut contact with the vessel wall (excluding those overlying side branches) in association with blood flow in between: it is synonymous with ‘stent malapposition’. A temporal classification identifies an acute and a late ISA. In the first case, ISA develops at the time of PCI as a result of a low implantation pressure or circular/focal calcifications that impede adequate stent expansion. Acute ISA is observed equally with bare metal stents (BMS) and DES, and is caused by a technique-dependent stent underexpansion. Its diagnosis requires a post-procedural intravascular imaging examination. Late ISA, diagnosed some time after the index procedure, is further divided into persistent and acquired. Persistent late ISA is due to unrecognized or untreated acute ISA that is revealed during a subsequent imaging study of the target lesion. In contrast, acquired late ISA is deemed as secondary to different phenomena such as increased vessel volume of the media without concomitant plaque or intima hyperplasia growth (‘positive remodelling’, the most common mechanism); thrombus dissolution or plaque dislodgement behind the stent struts with a consequent gap between stent and vessel wall (more likely if the stent was implanted in the setting of an acute coronary syndrome); and chronic stent recoil. Historically, definition of late ISA refers to the acquired type. Late ISA is more frequent after DES (10–20%) than after BMS (5–10%). Available findings from acute and late intravascular imaging studies show that persistent and acquired ISA contribute almost equally to late ISA.

There is great interest in investigating whether there is an association between ISA and stent thrombosis. A recent meta-analysis found a close correlation between late ISA and subsequent stent thrombosis among patients treated with DES. Nevertheless, it is still unclear whether different degrees of ISA impose different probabilities of adverse clinical events. Indeed, ISA appears to be a continuum from overt stent malapposition to aneurysm formation. Previously, Cook et al. found a very large ISA area (8.3 mm² on average) in patients experiencing very late stent thrombosis after DES. Thus, high grade ISA (probably ≥4 mm², in accordance with earlier data), rather than the presence/absence of ISA per se, would be associated with the hazard of abrupt thrombosis. Conversely, other data do not support this hypothesis. Another element to be considered is the finding suggesting that acquired
but not acute ISA correlates with the risk of late thrombotic events. This may indicate that the mechanisms responsible for the lost contact between stent struts and the vessel wall over time might be more important in generating the risk of stent thrombosis than the mere physical distance from the vessel wall.

Cook and colleagues have now shown the results of a prospective study involving 194 patients treated with either sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) in 221 coronary lesions. The study cohort comprised consecutive patients from those enrolled in the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial. The study design has two main elements: an 8-month IVUS investigation and a 5-year follow-up. ISA was present in 39 stented lesions (18%) of 37 patients. These patients compared with those without ISA showed a significantly increased risk of very late stent thrombosis (hazard ratio [HR] 23.2), myocardial infarction (HR 7.5), and major adverse cardiac events (HR 2.7). With an incidence of 27%, ISA was identified significantly more often in the SES group than in the PES group (9%). This is in line with the ISA incidence of 25% found in SES-treated patients in a previous series.

Caution is needed before considering the implications of this study. First, the study of Cook and colleagues, like almost all previous studies with intravascular imaging, is not sufficiently powered for the assessment of possible correlations with rare relevant events such as stent thrombosis or myocardial infarction. Secondly, the cohort of patients who underwent IVUS investigation at 8 months showed a lower risk profile than those who did not. This limitation is difficult to avoid in such studies. The design of the study requires an IVUS investigation to be done at 8 months in patients without thrombotic events up to this time point; this automatically excludes patients with higher risk more prone to develop these complications. Thirdly, the lack of an acute IVUS examination does not allow differentiation between persistent or acquired ISA as a cause of the late ISA. This differentiation might have further reduced the number of patients considered at an increased risk for stent thrombosis and improved the diagnostic specificity of the intravascular investigation. Fourthly, the lack of IVUS investigation at the time of very late stent thrombosis prevents the establishment of whether ISA was the sole mechanism responsible for the thrombotic event. Indeed, in the case of SES, stent fractures were found in the context of stent thrombosis. On the other hand, cases with resolution of ISA over time have also been reported for PES.

Finally, the possible contribution of neo-atherosclerosis might be defined, as in the case of late BMS thrombosis.

Stent thrombosis has always been a poorly understood, multifactorial complication and is even more so in the DES era. The
investigators from Bern do not claim to have fully clarified the mechanistic conundrum of very late stent thrombosis after DES; yet, they are to be commended for a carefully designed study that provides important mechanistic insights into local factors that drive the risk of this adverse event. The results presented are unique with respect to IVUS prediction of very late stent thrombosis after DES at extended follow-up. IVUS certainly remains a valuable method for examining the stent—vessel wall interface. Recent comparative studies have, however, shown that by virtue of its higher resolution, OCT is more sensitive than IVUS in identifying ISA and might also be able to identify thrombus deposition around the stent struts.25 Furthermore, the time is drawing nearer for a shift from the paradigm of physical measures (distance, coverage, thickness, areas, etc.) to specific morphological and functional features (neo-atherosclerosis, inflammation, etc.) of the stent—vessel interactions. New imaging modalities, such as micro-OCT26 and intravascular near-infrared fluorescence (NIRF),27 have the potential to assess coronary vessel wall response to DES in vivo. Micro-OCT is a new form of OCT that, by virtue of an unprecedented improvement in resolution, provides clear pictures of coronary artery cellular and subcellular microstructure, similarly to histopathology.26 Two-dimensional NIRF, through optical catheters and specific imaging agents, permits highly reliable spatial maps of vascular inflammatory processes.27 These techniques have the potential to represent a real step forward in unravelling the pathophysiology of DES-related phenomena. Figure 1 presents a collage of illustrations of the traditional and newer intravascular imaging techniques.

Although there is a widespread acceptance of the value of intravascular imaging as a prognostic factor, there is a critical need for generation of scientific evidence that these technologies may have therapeutic implications with a positive impact on patient outcomes. The most obvious field is the use of intravascular imaging during the procedure to guide the stent implantation technique with the goal of improving long-term stent patency. Many centres are using IVUS with this goal; however, studies with IVUS have not offered convincing evidence of a beneficial role. Newer imaging technologies may better meet our expectations in this regard. Indeed, an increasing amount of data, including those from the study of Cook and colleagues,20 points to a potential new role for intravascular imaging. If performed months after the procedure, it may predict the risk of very late stent thrombosis. Patients deemed at an excessive risk on the basis of this information may represent the target of a prolonged DAPT, whereas the vast majority of patients may safely discontinue the ADP receptor antagonist with the benefit of reducing the risk of bleeding and the costs of a longer term drug therapy. This hypothesized role needs to be proven by specifically designed studies. They will help not only to justify the costs associated with intravascular imaging but also to forestall the situation where an identified loss of stent contact with the vessel wall automatically means a signed contract with stent thrombosis.

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References

apposition after sirolimus-eluting stent implantation on 4-year clinical events: intravascular ultrasound analysis from the multicentre, randomised, RAVEL, E-SIRIUS and SIRIUS trials. Heart 2008;94:322–328.


A 39-year-old man with no clinical relevant data, elite long-distance runner, was admitted to our institution with the diagnosis of ventricular fibrillation while participating in a half-marathon competition. He was resuscitated at the site of the event with electrical cardioversion, and at his admission, he was clinically stable. Electrocardiogram demonstrated regular sinus rhythm. Echocardiography showed normal biventricular function and no presence of hypertrophic cardiomyopathy. Cardio-magnetic resonance demonstrated no findings of arrhythmogenic right ventricular dysplasia and no other pathological data. Electrocardiogram-gated 64-slice computed tomographic angiography (CTA) showed an anomalous origin of the right coronary artery (RCA) arising from the left coronary sinus with an intramural course (Panel A, arrow) between the aorta and pulmonary artery (Panel B).

Surgical translocation of the RCA was performed. With the use of extracorporeal circulation and cardioplegic arrest, the RCA was dissected distal to the intramural portion, all its way along the aortic root and initial part of the atroventricular groove (Panel C). Then, it was transected and the orifice of the intramural portion was closed. The RCA was anastomosed to the ascending aorta with a running 7/0 polypropylene suture. Post-operative course was uneventful. A CTA demonstrated successful reimplantation of the RCA in the right sinus (Panels D and E). On the 9th postoperative day, the patient was discharged home. Three months later, the patient was in NYHA class I. Ergometry examination results were satisfactory, with a peak of 15.2 METs. A single-photon emission tomography showed no myocardial ischaemia, and good left ventricular ejection fraction (62%).