

Drug Eluting Stents and Late Stent Thrombosis: Technical Considerations for Interventional Cardiologists

a report by

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Late stent thrombosis has been a concern for interventional cardiologists since the early days of drug-eluting stent (DES) technology. Although the problem did not appear common, a series of angiographically documented late stent thromboses from the Thoraxcenter Rotterdam was published in 2004, sounding a cautionary, albeit non-alarmist, note.¹ In 2005, a prospective observational cohort study of Taxus and Cypher DES cases, including 2,229 real world consecutive patients with 3,797 treated lesions, demonstrated higher than expected rates of stent thrombosis, with a sub-acute or late stent thrombosis cumulative incidence of 1.3% at nine months post-procedure.² Predictors of thrombosis were premature discontinuation of anti-platelet therapy, renal failure, bifurcation lesions and diabetes. The issue gained momentum following the European Society of Cardiology/World Congress of Cardiology meeting in Barcelona in September 2006, during which data was presented suggesting late stent thrombosis could be a greater problem than had previously been recognised. This material took the form of a meta-analysis of the first generation Sirolimus and Paclitaxel stent trials, including the Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Sten (RAVEL), Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS), European (E)-SIRIUS, Canadian (C)-SIRIUS and Taxus II, IV, V and VI programmes. Although the methodology has been criticised, the data presented does raise some concerns that late stent thrombosis might be both under-recognised and significantly more of a problem with DES than with bare metal stents (BMS).³ Subsequently, the fast-tracked publication of the Basel Stent Cost-effectiveness Trial-Late Thrombotic Events (BASKET-Late) trial revealed a 'catch-up' phenomenon of late events, whereby patients randomly assigned to DES therapy exhibited higher rates of death and non-fatal myocardial infarction (MI) in the 12 months after stopping clopidogrel therapy than those assigned to BMS therapy.⁴ Separate datasets from the major Cypher and Taxus trials, presented at the October 2006 TCT meeting appeared reassuring, although there were small but statistically significant increases in late stent thrombosis of 0.5% (Taxus) and 0.6% (Cypher) between years one and four of follow-

up compared with bare metal stent cases.^{5,6} However, the most impressive aspect of these studies was evidence of sustained and marked reductions in the need for target lesion and vessel revascularisation in DES cases. In November 2006, separate large meta-analyses from different sources were published in the *European Heart Journal*, resulting in different conclusions but revealing some subtle and very interesting issues relating to event adjudication and statistical analysis.⁷⁻⁹ Even if we take the more reassuring data at face value, it must be recognised that current randomised trial data is comprised of relatively short-term follow-up of patients who underwent treatment of relatively simple lesions, with the exception of some of the Taxus trial patients. Two very important issues must be noted. Firstly, real-world practice inevitably involves treatment of more complex lesions than would be included in randomised trials, and many characteristics of complex lesions can be expected to make focal under-deployment and mal-apposition of stent struts more likely. Secondly, it appears logical that the risk of late stent thrombosis, especially once dual anti-platelet therapy has been stopped, is cumulative with time, making follow-up periods of two or three years falsely reassuring. The reason for this is that the presumed focal point for thrombotic occlusion persists in the form of non-endothelialised stent struts protruding into the arterial lumen.

While it does seem that there is at present little danger of an epidemic of late stent thrombosis, cardiologists must do all within their power to ensure this problem remains small. The most important headline message should be that dual anti-platelet therapy must be continued for at least the minimum prescribed period, and possibly much longer. On a more technical level, paying attention to the basic principles and techniques of coronary stent placement is a very important way to minimise this risk of late stent thrombosis.

Well-deployed stents, with good apposition against the arterial wall, covering the entire coronary lesion have long been accepted as conferring reduced risk of acute complications in coronary intervention. Early stent era data suggested that this level of stent deployment, as evidenced by intravascular ultrasound

(IVUS) examination, would reduce acute stent thrombosis.¹⁰ However, the advent of powerful anti-platelet therapy, such as combined Aspirin and Clopidogrel, and glycoprotein 2b3a inhibitors, made acute stent thrombosis much less of an issue, and left the remaining problem of in-stent restenosis the 'Achilles Heel' of stent technology. The incidence of in-stent restenosis was dramatically and quite suddenly cut with the arrival of DES, and many randomised controlled trial and real-world registry datasets emerged to support widespread use of these devices. DES technology translated into excellent angiographic outcomes in the form of marked reductions in late loss and binary restenosis as well as the all-important reductions in adverse clinical outcomes, such as target lesion and vessel revascularisation. A possible consequence of reduced immediate procedural complications and reduced in-stent restenosis is a drift away from meticulous attention to stent deployment, which had been perceived as absolutely mandatory in the bare metal stent era. This could clearly increase the chances of late stent thrombosis, particularly after cessation of up to 12 months of dual anti-platelet therapy. Bare metal stents are theoretically less likely to carry such a late risk, as the restenosis process could reasonably be expected to cover stent struts. It is therefore more important than ever for interventional cardiologists to ensure optimal coronary stent implantation. Technical considerations to this end fall under the broad headings of lesion assessment, lesion preparation, stent deployment and post-dilatation.

Lesion Assessment

It is abundantly clear that certain coronary artery and lesion characteristics influence the likelihood of adequate stent deployment. Examples of such characteristics include long, calcified and complex lesions in tortuous vessels. A thorough appreciation of the impact of these features on late events is required, and careful angiographic assessment of vessel and lesion features prior to stent selection is important. However, angiographic assessment of coronary disease leads to under-estimation of both reference vessel size and atherosclerotic burden. These aspects of coronary disease can be appreciated readily with IVUS examination,¹¹ which adds relatively little procedural time and has a low complication rate.¹²

Lesion Preparation and Stent Deployment

Different coronary lesions respond in different ways to stent deployment. Knowing how a coronary stenosis is likely to respond is therefore crucial if good stent deployment is to be achieved as a final result. Soft

compliant lesions may need no preparation prior to stent deployment. Indeed, pre-dilatation of some lesion types, such as soft thrombus laden stenoses in acute coronary syndrome and ST-elevation MI, increases the likelihood of adverse outcomes.¹³ However, calcified or densely fibrotic lesions often require extensive pre-dilatation, and heavily calcified disease may well require atherectomy-based techniques. In the absence of these characteristics, direct stenting has been shown in randomised trials to be appropriate.^{14,15}

Stents need to be selected according to a number of lesion and vessel factors. Most obvious of these is the requirement for the stent and reference vessel diameters to be appropriately correlated. This can be achieved by careful angiographic and IVUS evaluation, but knowledge of the extent to which nominal stent size can be influenced by higher or lower inflation pressure *in vivo* is also important. Often, the reference vessel diameter can change significantly along the proposed stent length, requiring an initially low inflation pressure and later post-dilatation with larger balloons at higher pressure within larger vessel sections. Once the deployment has begun, the profile of the inflated stent-balloon unit should be studied closely, looking for adequate sizing and contour defects that may indicate a need for more in-stent ballooning. It is important to be aware that the post-deployment angiogram can look deceptively good within the stented region despite under-deployment, due to contrast dye tracking between the stent and vessel wall. By the same token, the post-deployment angiogram is important in detecting over-inflation, which can increase the chance of immediate and delayed complications, due to problems such as stent edge dissection. It is often the case that such stent deployment imperfections can be found on IVUS examination, but not on angiographic assessment.¹⁶ There is data to support the use of IVUS to guide optimal stent deployment¹⁷ and that this reduces later complications.^{18,19}

Post Dilatation

In order to chase the goal of optimal stent implantation, post-dilatation is usually necessary. For this, it is important to identify regions within the stented segment that display marked stent asymmetry, inadequate stent expansion and poor apposition to the arterial wall. IVUS is the gold standard for this type of assessment, and inadequate IVUS measured lumen area post-stenting predicts late stent thrombosis.²⁰ It is usually necessary for a larger and non-compliant angioplasty balloon to be used for post-dilatation purposes, and high inflation pressures are the rule rather than the exception. It is interesting to note that perfect stent deployment can seldom be achieved.¹⁹ This fact, combined with the

phenomenon of late positive remodelling, could theoretically increase the risk of very late complications associated with DES use.

Summary

Although there are some concerns about late stent thrombosis, the incidence of this problem remains, as far as can be ascertained, very low. By taking into

account lesion characteristics, the need for adequate lesion preparation, the stent size and required inflation pressure, and the need for post-dilatation to optimise deployment, it should be possible to keep the problem of late stent thrombosis at bay. The most useful practical tool in this respect is intravascular ultrasound, and the most important pharmacological accompaniment is an adequate duration of dual anti-platelet therapy. ■

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